Clin Exp Nephrol (2003) 7:255–259
DOI 10.1007/s10157-003-0259-6

REVIEW ARTICLE

Katsuhiko Asanuma · Peter Mundel

The role of podocytes in glomerular pathobiology

Received: September 29, 2003 / Accepted: October 5, 2003

Abstract
Podocytes are unique cells with a complex cellular organization. With respect to their cytoarchitecture, podocytes may be divided into three structurally and functionally different segments: cell body, major processes, and foot processes (FPs). The FPs of neighboring podocytes regularly interdigitate, leaving between them the filtration slits that are bridged by an extracellular structure, known as the slit diaphragm (SD). Podocytes cover the outer aspect of the glomerular basement membrane (GBM). They therefore form the final barrier to protein loss, which explains why podocyte injury is typically associated with marked proteinuria. Chronic podocyte injury may lead to podocyte detachment from the GBM. Our knowledge of the molecular structure of the SD has been remarkably improved in the past few years. Several molecules, including nephrin, CD2AP, FAT, ZO-1, P-cadherin, Podocin, and Neph 1-3 have all been shown to be associated with the SD complex, and some of these molecules are critical for its integrity. Podocytes are injured in many forms of human and experimental glomerular disease. The early events are characterized either by alterations in the molecular composition of the SD without visible changes in morphology or, more obviously, by a reorganization of FP structure with the fusion of filtration slits and the apical displacement of the SD. Based on recent insights into the molecular pathology of podocyte injury, at least four major causes have been identified that lead to the uniform reaction of FP effacement and proteinuria: (1) interference with the SD complex and its lipid rafts; (2) direct interference with the actin cytoskeleton; (3) interference with the GBM or with podocyte-GBM interaction; and (4) interference with the negative surface charge of podocytes. There is also evidence, in focal segmental glomerular sclerosis (FSGS) and in idiopathic nephrotic syndrome in humans and rats, that podocyte damage may be caused by circulating albuminuric factors. Ongoing studies in many laboratories are aiming at an understanding of the dynamic relationship between SD proteins, the actin cytoskeleton, and the dynamics of FP structure in nephrotic syndrome and FSGS. These studies should provide us with a better understanding of the biological mechanism underlying the podocyte response to injury. Such studies will potentially translate into more refined treatment and the prevention of proteinuria and progressive glomerular disease.

Key words Focal segmental glomerulosclerosis · Glomerulus · Nephrotic syndrome · Proteinuria · Slit diaphragm

K. Asanuma · P. Mundel (✉)
Division of Nephrology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA
Tel. +1-718-430-3219; Fax +1-718-430-8963
e-mail: mundel@aecom.yu.edu

K. Asanuma
Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan

Podocyte structure

The glomerular basement membrane (GBM) provides the primary structural support for the glomerular tuft. The basic unit of the glomerular tuft is a single capillary. Endothelial and mesangial cells are located inside the GBM, while podocytes are attached to its outer aspect.[1] Podocytes are unique cells with a complex cellular organization. With respect to their cytoarchitecture, podocytes may be divided into three structurally and functionally different segments: cell body, major processes, and foot processes (FPs). Cell bodies and major processes are generally not directly attached to the GBM, but float freely in the filtrate in Bowman's space, leaving a "sub-cell body space" between the cell body, and the FP. From the cell body, major processes arise that, directly or after additional branching, split into FPs. The FPs of neighboring podocytes regularly interdigitate, leaving between them the filtration slits that are bridged by an extracellular structure, known as the slit diaphragm (SD). In the FP, a complete microfilament-based contractile apparatus is present. This system is composed of actin, myosin II, α-actinin, talin, and vinculin.[1] The FP

is fixed to the GBM via α3β1-integrin[2] and α-/β-dystroglycans.[3,4] Recently, it has also been reported that integrin-α5[5] and -β4[6] are found along the surfaces of podocytes on the GBM. α3β1-Integrin is major integrin expressed by podocytes. The importance of α3β1-integrin in podocyte differentiation first became apparent when knockout of the α3 integrin gene resulted in an inability to assemble FPs, and α3β1-integrin deficient mice did not survive for more than a few hours after birth, most likely due to glomerular dysfunction.[7] In α3β1-integrin deficient mice, the GBM was disorganized and podocytes were unable to form mature FPs. Currently, downstream signaling events are being elucidated, concentrating mainly on integrin-dependent cascades and their consequences for podocyte adhesion and proliferation.[8] A second matrix receptor in podocytes, the dystroglycan complex, is known to provide a molecular link between matrix molecules and the actin cytoskeleton in a variety of cells. Expression of the dystroglycan complex is restricted to the basal cell membrane of podocyte FPs.[3,4] Expression of the dystroglycan complex is negatively correlated with disease activity in proteinuria in animal models[4] and with minimal-change disease (MCD) in humans.[3]

The slit diaphragm complex: a dynamic site of glomerular permselectivity

In the mature kidney, the SD is the only site of cell-cell contact between the FPs of adjacent podocytes. The SD appears as a tiny membrane bridging the 30- to 40-nm wide filtration slit. In 1974, Rodewald and Karnovsky showed, by transmission electron microscopy, that the SD was made up of rod-like units connected in the center to a linear bar forming a zipper-like appearance, but the nature of the components of the SD and its anchorage in the FP had been unclear for a long time.[1] Our knowledge of the molecular structure of the SD has been remarkably improved in the past few years. A growing number of proteins, including nephrin,[9–11] CD2AP,[12–14] FAT,[15,16] ZO-1,[17] P-cadherin,[18] Podocin,[19] and Neph 1–3[20–22] have all been shown to be expressed within the SD complex, and some of these molecules play a major role in maintaining the structural and functional integrity of the SD complex.

The nephrin gene, *NPHS1*, is the target gene of congenital nephrotic syndrome of Finnish type.[23,24] The respective gene product of *NPHS1*, nephrin, a 180-kDa transmembrane protein, is exclusively expressed by podocytes within the kidney and is predominantly localized to the SD.[9] Inactivation of *NPHS1* in mice results in proteinuria and partial FP effacement.[25] Similarly, the injection of anti-nephrin antibody 5-1-6 causes proteinuria.[26,27] Nephrin oligomers associate within lipid rafts signaling microdomains of the SD.[22] The injection of anti-podocyte ganglioside antibody leads to FP effacement, tyrosine phosphorylation, and the relocation of nephrin to the apical pole of the narrowed filtration slits.[28] Redistribution of nephrin on the luminal side of podocytes has been described in acquired human nephrotic syndrome.[29,30] The expression of nephrin in human diabetic nephropathy is downregulated by glycated albumin and angiotensin II.[31] On the other hand, circulating vascular endothelial growth factor (VEGF) and all-trans-retinoic acid (ATRA) are important to maintain the expression of nephrin.[32,33] The proinflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)α can also upregulate nephrin expression in vitro.[34] The upregulation of nephrin may indicate a cross-communication between immune cells and podocytes controlling podocyte functionality.

A homologue of nephrin, *NEPH-1*, was recently discovered using retrovirus-mediated mutagenesis. Disruption of the *NEPH-1* gene in mice results in effacement of podocytes, heavy proteinuria, and early postnatal death.[20] Like nephrin, NEPH-1 is a transmembrane protein of the Ig superfamily, strongly expressed by podocytes,[21] and it localizes to the SD.[35] Nephrin and Neph1 colocalize at the SD and form homo- and heterodimers.[36] Neph1 also interacts with podocin[21] and ZO-1.[37] These findings suggest that NEPH1 plays also an important role in maintaining the structure of the glomerular filter.

At the intracellular insertion site of the SD, the adapter protein CD2AP has been localized. This protein was originally discovered as a protein interacting with the CD2 receptor in T-lymphocytes.[38] In the kidney, CD2AP is primarily expressed in podocytes, but not in glomerular endothelial or mesangial cells. Mice completely lacking CD2AP die of massive proteinuria shortly after birth, suggesting an important role for CD2AP in the filtration apparatus of the kidney.[13] CD2AP is also involved in endocytosis.[39] CD2AP heterozygous mice are prone to glomerular disease.[40] They also show defects in the formation of multivesicular bodies, suggesting an impairment of the intracellular degradation pathway in podocytes.[40] CD2AP directly associates with actin,[41] nephrin,[12] and podocin.[14]

ZO-1 is located on foot processes at the insertions of the SDs.[17] ZO-1 interacts with the actin-based cytoskeleton and may also participate in signaling events through tyrosine phosphorylation.[42] The PDZ domain protein of ZO-1 binds to the C-terminus of Neph family members.[37] Spontaneously proteinuric Munich-Wistar-Froemter rats have normal podocyte foot processes and SDs, with the only apparent defect being a redistribution of ZO-1 in the cytoplasm and cytoplasmic surface of the cell membrane.[43] Treatment with angiotensin-converting enzyme (ACE) inhibitors ameliorates the proteinuria and restores the normal localization of ZO-1 at the SD in these spontaneously proteinuric Munich-Wistar-Froemter rats.[43]

mFAT1 is a nonclassical giant protocadherin. In podocytes, mFAT1 is localized to the SD.[15] Mice lacking mFAT1 exhibit perinatal lethality, most probably caused by loss of the glomerular SD and fusion of podocyte FPs.[16] These data confirm a necessary role for mFAT1 in the development of the SD.

Mutation of *NPHS2* is the genetic cause of autosomal recessive, steroid-resistant nephrotic syndrome in some patients,[44] and it may also cause sporadic focal segmental glomerular sclerosis (FSGS).[45–52] The *NPHS2* gene product,

podocin, is a new member of the stomatin family and localizes to the podocyte FP membrane, at the insertion site of the slit diaphragm.[14,19] Podocin oligomerizes in lipid rafts and associates with CD2AP and nephrin.[14] Podocin may also facilitate nephrin signaling.[53] In puromycin aminonucleoside (PAN) nephropathy, podocin relocates to newly formed tight junctions.[54] Podocin may act as a scaffolding protein, serving in the structural organization of the SD and the regulation of its filtration function.

Transcriptional control of podocyte differentiation and function

Recent findings from various transgenic and knockout mouse models, and the identification of genes responsible for human podocyte disease, have provided insight into the transcriptional regulation of some of the processes in such diseases. The transcriptional factors involved include *Pax2*, *WT1* (the Wilms tumor suppressor gene), *Pod1* (capsulin, epicardin), kreisler (*maf-1*), *lmx1b*, and *Mf2*.[55] Kreisler null mice develop proteinuria and FP effacement. Kreisler acts between the capillary loop and mature stages and downstream of *Pod1*. Podocin and nephrin are slightly reduced in kreisler null podocytes.[56] However, these observations alone are unlikely to account for aberrant podocyte foot process formation. Thus, kreisler must regulate other (unknown?) genes required for podocyte function. It will be very interesting to determine whether reduced kreisler expression is involved in acquired forms of FP effacement, e.g., in MCD.

Lmx1b was identified as the gene that was mutated in nail-patella syndrome, an autosomal dominant disease with skeletal abnormalities, nail hypoplasia, and nephropathy.[57,58] *Lmx1b* knockout mice show decreasing expression of GBM collagens and impaired differentiation of podocytes.[59,60] Furthermore, *Lmx1b* regulates the expression of multiple podocyte genes, *CD2AP* and *NPHS2* (podocin), critical for podocyte differentiation and function.[60] *Mf2* (mesoderm/mesenchyme forkhead 2) encodes a forkhead/winged helix transcription factor expressed in numerous tissues of the mouse embryo, including the developing kidney.[61] *Mf2* is expressed in the podocytes of developing and mature glomeruli from the late S-shaped stage onwards.[61] Although null *Mf2* mice have developed renal defects, no abnormalities specific to the podocyte have been described.[61]

The role of podocyte injury in glomerular diseases

Podocytes are injured in many forms of human and experimental glomerular disease, including MCD, focal segmental glomerulosclerosis, membranous glomerulopathy, diabetes mellitus, and lupus nephritis.[62,63] The early events are characterized either by alterations in the molecular composition of the SD without visible changes in morphology or, more obviously, by a reorganization of FP structure with the fusion of filtration slits and apical displacement of the SD.[62,63] Effacement of the FP is accompanied by a reorganization of the actin cytoskeleton into a dense network,[64] which is preceded by the induction of the podocyte α-actinin-4 molecule,[65] an actin filament cross-linker with an important function in podocytes.[66,67] α-Actinin-4 is a member of the actinin family of actin-filament cross-linking proteins.[68] In the glomerulus, α-actinin-4 is exclusively expressed in podocytes, and mutations in the *ACTN4* gene, encoding α-actinin-4, cause familial FSGS, presenting at variable time points of disease onset effacement.[67] Mice deficient in α-actinin-4 show progressive proteinuria and focal segmental sclerosis.[69] The Rho small G protein family is an important mediator of actin cytoskeletal reorganization that results in changes in the morphology, motility, and adhesion of cells. Mice lacking Rho GDIα developed massive proteinuria mimicking nephritic syndrome, suggesting that the Rho family is important to maintain the FP.[70] These findings indicate that an inherited defect of the podocyte actin cytoskeleton itself is involved in the pathogenesis of proteinuria and glomerulosclerosis.

Major causes of podocyte injury

Based on recent insights into the molecular pathology of podocyte injury, at least four major causes have been identified that lead to the uniform reaction of FP effacement and proteinuria: (i) interference with the SD complex and its lipid rafts; (ii) direct interference with the actin cytoskeleton; (iii) interference with the GBM or with podocyte-GBM interaction; and (iv) interference with the negative surface charge of podocytes or with the activity of GLEPP1, a membrane-bound tyrosin phosphatase. There is also evidence, in FSGS and in idiopathic nephrotic syndrome in humans and rats, that podocyte damage may be caused by circulating albuminuric factors.[71,72]

The role of podocytes in the progression of glomerular diseases

From the viewpoint of progressive glomerular disease, it is important to recognize that if the early structural changes are not reversed, severe and progressive glomerular damage develops. This involves: (a) cell-body attenuation; (b) pseudocyst formation and vacuolization; (c) detachment from the GBM, resulting in podocyte depletion; (d) cell hypertrophy, but no cell proliferation and also cell death; and (e) the formation of synechiae by the attachment of parietal epithelial cells to denuded GBM.[73] These events underlie the formation of synechiae via the attachment of parietal epithelial cells of Bowman's capsule to denuded GBM areas. These changes are irreversible, and ultimately lead to the development of glomerulosclerosis and endstage renal failure.[74] Studies in human type I and II diabetic nephropathy,[75–77] in IgA nephropathy,[78] in the chronic puromycin

model of glomerulosclerosis,[79] and in transforming growth factor (TGF)-β transgenic mice[80] collectively provide convincing evidence for a correlation between the loss of podocytes and the progression of glomerular diseases.

Ongoing studies in many laboratories are aiming at an understanding of the dynamic relationship between SD proteins, the actin cytoskeleton, and the dynamics of FP structure in nephrotic syndrome and FSGS. These studies should provide us with a better understanding of the biological mechanism underlying the podocyte response to injury. Such studies will potentially translate into more refined treatment and the prevention of proteinuria and progressive glomerular disease.

Acknowledgments K.A. is supported by a fund from the Alumni Association of Juntendo University and a personal grant from Professor Yasuhiko Tomino (Division of Nephrology, Department of Internal Medicine, Juntendo University). P.M. is supported by grants from the NIH/NIDDK.

References

1. Mundel P, Kriz W. Structure and function of podocytes: an update. Anat Embryol (Berl) 1995;192:385–97.
2. Adler S. Characterization of glomerular epithelial cell matrix receptors. Am J Pathol 1992;141:571–8.
3. Regele HM, Fillipovic E, Langer B, Poczewki H, Kraxberger I, Bittner RE, et al. Glomerular expression of dystroglycans is reduced in minimal change nephrosis but not in focal segmental glomerulosclerosis. J Am Soc Nephrol 2000;11:403–12.
4. Raats CJ, van Den Born J, Bakker MA, Oppers-Walgreen B, Pisa BJ, Dijkman HB, et al. Expression of agrin, dystroglycan, and utrophin in normal renal tissue and in experimental glomerulopathies. Am J Pathol 2000;156:1749–65.
5. Mayer G, Boileau G, Bendayan M. Furin interacts with proMT1-MMP and integrin alphaV at specialized domains of renal cell plasma membrane. J Cell Sci 2003;116:1763–73.
6. Kambham N, Tanji N, Seigle RL, Markowitz GS, Pulkkinen L, Uitto J, et al. Congenital focal segmental glomerulosclerosis associated with beta4 integrin mutation and epidermolysis bullosa. Am J Kidney Dis 2000;36:190–6.
7. Kreidberg JA, Donovan MJ, Goldstein SL, Rennke H, Shepherd K, Jones RC, et al. Alpha 3 beta 1 integrin has a crucial role in kidney and lung organogenesis. Development 1996;122:3537–47.
8. Kretzler M, Teixeira VP, Unschuld PG, Cohen CD, Wanke R, Edenhofer I, et al. Integrin-linked kinase as a candidate downstream effector in proteinuria. FASEB J 2001;15:1843–5.
9. Ruotsalainen V, Ljungberg P, Wartiovaara J, Lenkkeri U, Kestil M, Jalanko H, et al. Nephrin is specifically located at the slit diaphragm of glomerular podocytes. Proc Natl Acad Sci U S A 1999;96:7962–7.
10. Holthofer H, Ahola H, Solin ML, Wang S, Palmen T, Luimula P, et al. Nephrin localizes at the podocyte filtration slit area and is characteristically spliced in the human kidney. Am J Pathol 1999;155:1681–7.
11. Holzman LB, John PL, Kovari IA, Verma R, Holthofer H, Abrahamson DR. Nephrin localizes to the slit pore of the glomerular epithelial cell. Kidney Int 1999;56:1481–91.
12. Shih NY, Li J, Cotran R, Mundel P, Miner JH, Shaw AS. CD2AP Localizes to the slit diaphragm and binds to nephrin via a novel C-terminal domain. Am J Pathol 2001;159:2303–8.
13. Shih NY, Li J, Karpitskii V, Nguyen A, Dustin ML, Kanagawa O, et al. Congenital nephrotic syndrome in mice lacking CD2-associated protein. Science 1999;286:312–5.
14. Schwarz K, Simons M, Reiser J, Saleem MA, Faul C, Kriz W, et al. Podocin, a raft-associated component of the glomerular slit diaphragm, interacts with CD2AP and nephrin. J Clin Invest 108:1621–9.
15. Inoue T, Yaoita E, Kurihara H, Shimizu F, Sakai T, Kobayashi T, et al. FAT is a component of glomerular slit diaphragms. Kidney Int 2001;59:1003–12.
16. Ciani L, Patel A, Allen ND, Ffrench-Constant C. Mice lacking the giant protocadherin mFAT1 exhibit renal slit junction abnormalities and a partially penetrant cyclopia and anophthalmia phenotype. Mol Cell Biol 2003;23:3575–82.
17. Schnabel E, Anderson JM, Farquhar MG. The tight junction protein ZO-1 is concentrated along slit diaphragms of the glomerular epithelium. J Cell Biol 1990;111:1255–63.
18. Reiser J, Kriz W, Kretzler M, Mundel P. The glomerular slit diaphragm is a modified adherens junction. J Am Soc Nephrol 2000;11:1–8.
19. Roselli S, Gribouval O, Boute N, Sich M, Benessy F, Attie T, et al. Podocin localizes in the kidney to the slit diaphragm area. Am J Pathol 2002;160:131–9.
20. Donoviel DB, Freed DD, Vogel H, Potter DG, Hawkins E, Barrish JP, et al. Proteinuria and perinatal lethality in mice lacking neph1, a novel protein with homology to nephrin. Mol Cell Biol 2001;21:4829–36.
21. Sellin L, Huber TB, Gerke P, Quack I, Pavenstadt H, Walz G. NEPH1 defines a novel family of podocin interacting proteins. FASEB J 2003;17:115–7.
22. Barletta GM, Kovari IA, Verma RK, Kerjaschki D, Holzman LB. Nephrin and Neph1 co-localize at the podocyte foot process intercellular junction and form cis hetero-oligomers. J Biol Chem 2003; 278:19266–71.
23. Kestila M, Lenkkeri U, Mannikko M, Lamerdin J, McCready P, Putaala H, et al. Positionally cloned gene for a novel glomerular protein – nephrin – is mutated in congenital nephrotic syndrome. Mol Cell 1998;1:575–82.
24. Lenkkeri U, Mannikko M, McCready P, Lamerdin J, Gribouval O, Niaudet PM, et al. Structure of the gene for congenital nephrotic syndrome of the Finnish type (NPHS1) and characterization of mutations. Am J Hum Genet 1999;64:51–61.
25. Putaala H, Soininen R, Kilpelainen P, Wartiovaara J, Tryggvason K. The murine nephrin gene is specifically expressed in kidney, brain and pancreas: inactivation of the gene leads to massive proteinuria and neonatal death. Hum Mol Genet 2001;10:1–8.
26. Orikasa M, Matsui K, Oite T, Shimizu, F. Massive proteinuria induced in rats by a single intravenous injection of a monoclonal antibody. J Immunol 1988;141:807–14.
27. Topham PS, Kawachi H, Haydar SA, Chugh S, Addona TA, Charron KB, et al. Nephritogenic mAb 5-1-6 is directed at the extracellular domain of rat nephrin. J Clin Invest 1999;104:1559–66.
28. Simons M, Schwarz K, Kriz W, Miettinen A, Reiser J, Mundel P, et al. Involvement of lipid rafts in nephrin phosphorylation and organization of the glomerular slit diaphragm. Am J Pathol 2001;159:1069–77.
29. Wernerson A, Duner F, Pettersson E, Widholm SM, Berg U, Ruotsalainen V, et al. Altered ultrastructural distribution of nephrin in minimal change nephrotic syndrome. Nephrol Dial Transplant 2003;18:70–6.
30. Doublier S, Ruotsalainen V, Salvidio G, Lupia E, Biancone L, Conaldi PG, et al. Nephrin redistribution on podocytes is a potential mechanism for proteinuria in patients with primary acquired nephrotic syndrome. Am J Pathol 2001;158:1723–31.
31. Doublier S, Salvidio G, Lupia E, Ruotsalainen V, Verzola D, Deferrari G, et al. Nephrin expression is reduced in human diabetic nephropathy: evidence for a distinct role for glycated albumin and angiotensin II. Diabetes 2003;52:1023–30.
32. Sugimoto H, Hamano Y, Charytan D, Cosgrove D, Kieran M, Sudhakar A, et al. Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. J Biol Chem 2003;278:12605–8.
33. Suzuki A, Ito T, Imai E, Yamato M, Iwatani H, Kawachi H, et al. Retinoids regulate the repairing process of the podocytes in puromycin aminonucleoside-induced nephrotic rats. J Am Soc Nephrol 2003;14:981–91.
34. Huwiler A, Ren S, Holthofer H, Pavenstadt H, Pfeilschifter J. Inflammatory cytokines upregulate nephrin expression in human embryonic kidney epithelial cells and podocytes. Biochem Biophys Res Commun 2003;305:136–42.

35. Liu G, Kaw B, Kurfis J, Rahmanuddin S, Kanwar YS, Chugh SS. Neph1 and nephrin interaction in the slit diaphragm is an important determinant of glomerular permeability. J Clin Invest 2003;112:209–21.
36. Gerke P, Huber TB, Sellin L, Benzing T, Walz G (2003) Homodimerization and heterodimerization of the glomerular podocyte proteins nephrin and NEPH1. J Am Soc Nephrol 14:918–926.
37. Huber TB, Schmidts M, Gerke P, Schermer B, Zahn A, Hartleben B, et al. The carboxy terminus of Neph family members binds to the PDZ domain protein zonula occludens-1. J Biol Chem 2003;278:13417–21.
38. Dustin ML, Olszowy MW, Holdorf AD, Li J, Bromley S, Desai N, et al. A novel adapter protein orchestrates receptor patterning and cytoskeletal polarity in T-cell contacts. Cell 1998;94:667–77.
39. Cormont M, Meton I, Mari M, Monzo P, Keslair F, Gaskin C, et al. CD2AP/CMS Regulates endosome morphology and traffic to the degradative pathway through its interaction with Rab4 and c-Cbl. Traffic 2003;4:97–112.
40. Kim JM, Wu H, Green G, Winkler CA, Kopp JB, Miner JH, et al. CD2-associated protein haploinsufficiency is linked to glomerular disease susceptibility. Science 2003;300:1298–300.
41. Lehtonen S, Zhao F, Lehtonen E. CD2-associated protein directly interacts with the actin cytoskeleton. Am J Physiol Renal Physiol 2002;283:F734–43.
42. Kurihara H, Anderson JM, Farquhar MG. Increased Tyr phosphorylation of ZO-1 during modification of tight junctions between glomerular foot processes. Am J Physiol 1995;268:F514–24.
43. Macconi D, Ghilardi M, Bonassi ME, Mohamed EI, Abbate M, Colombi F, et al. Effect of angiotensin-converting enzyme inhibition on glomerular basement membrane permeability and distribution of zonula occludens-1 in MWF rats. J Am Soc Nephrol 2000;11:477–89.
44. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. Nat Genet 2000;24:349–54.
45. Caridi G, Bertelli R, Scolari F, Sanna-Cherchi S, Di Duca M, Ghiggeri GM. Podocin mutations in sporadic focal-segmental glomerulosclerosis occurring in adulthood. Kidney Int 2003;64:365.
46. Bertelli R, Ginevri F, Caridi G, Dagnino M, Sandrini S, Di Duca M, et al. Recurrence of focal segmental glomerulosclerosis after renal transplantation in patients with mutations of podocin. Am J Kidney Dis 2003;41:1314–21.
47. Caridi G, Bertelli R, Di Duca M, Dagnino M, Emma F, Onetti Muda A, et al. Broadening the spectrum of diseases related to podocin mutations. J Am Soc Nephrol 2003;14:1278–86.
48. Maruyama K, Iijima K, Ikeda M, Kitamura A, Tsukaguchi H, Yoshiya K, et al. NPHS2 mutations in sporadic steroid-resistant nephrotic syndrome in Japanese children. Pediatr Nephrol 2003;18:412–6.
49. Tesar V, Zima T, Kalousova M. Pathobiochemistry of nephrotic syndrome. Adv Clin Chem 2003;37:173–218.
50. Komatsuda A, Wakui H, Maki N, Kigawa A, Goto H, Ohtani H, et al. Analysis of mutations in alpha-actinin 4 and podocin genes of patients with chronic renal failure due to sporadic focal segmental glomerulosclerosis. Ren Fail 2003;25:87–93.
51. Winn MP. Not all in the family: mutations of podocin in sporadic steroid-resistant nephrotic syndrome. J Am Soc Nephrol 2002;13:577–9.
52. Karle SM, Uetz B, Ronner V, Glaeser L, Hildebrandt F, Fuchshuber A. Novel mutations in NPHS2 detected in both familial and sporadic steroid-resistant nephrotic syndrome. J Am Soc Nephrol 2002;13:388–93.
53. Huber TB, Kottgen M, Schilling B, Walz G, Benzing T. Interaction with podocin facilitates nephrin signaling. J Biol Chem 2001;276:41543–6.
54. Kawachi H, Koike H, Kurihara H, Sakai T, Shimizu F. Cloning of rat homologue of podocin: expression in proteinuric states and in developing glomeruli. J Am Soc Nephrol 2003;14:46–56.
55. Quaggin SE. Transcriptional regulation of podocyte specification and differentiation. Microsc Res Tech 2002;57:208–11.
56. Sadl V, Jin F, Yu J, Cui S, Holmyard D, Quaggin S, Barsh G, Cordes S (2002) The mouse Kreisler (Krml1/MafB) segmentation gene is required for difrerentiation of glomerular visceral epithelial cells. Dev Biol 249:16–29.
57. Morello R, Lee B. Insight into podocyte differentiation from the study of human genetic disease: nail-patella syndrome and transcriptional regulation in podocytes. Pediatr Res 2002;51:551–8.
58. Morello R, Zhou G, Dreyer SD, Harvey SJ, Ninomiya Y, Thorner PS, et al. Regulation of glomerular basement membrane collagen expression by LMX1B contributes to renal disease in nail-patella syndrome. Nat Genet 2001;27:205–8.
59. Rohr C, Prestel J, Heidet L, Hosser H, Kriz W, Johnson RL, et al. The LIM-homeodomain transcription factor Lmx1b plays a crucial role in podocytes. J Clin Invest 2002;109:1073–82.
60. Miner JH, Morello R, Andrews KL, Li C, Antignac C, Shaw AS, et al. Transcriptional induction of slit diaphragm genes by Lmx1b is required in podocyte differentiation. J Clin Invest 2002;109:1065–72.
61. Kume T, Deng K, Hogan BL. Minimal phenotype of mice homozygous for a null mutation in the forkhead/winged helix gene, Mf2. Mol Cell Biol 2000;20:1419–25.
62. Somlo S, Mundel P. Getting a foothold in nephrotic syndrome. Nat Genet 2000;24:333–5.
63. Kerjaschki D. Caught flat-footed: podocyte damage and the molecular bases of focal glomerulosclerosis. J Clin Invest 2001;108:1583–7.
64. Shirato I, Sakai T, Kimura K, Tomino Y, Kriz W. Cytoskeletal changes in podocytes associated with foot process effacement in Masugi nephritis. Am J Pathol 1996;148:1283–96.
65. Smoyer WE, Mundel P, Gupta A, Welsh MJ. Podocyte alpha-actinin induction precedes foot process effacement in experimental nephrotic syndrome. Am J Physiol 1997;273:F150–7.
66. Kaplan J, Pollak MR. Familial focal segmental glomerulosclerosis. Curr Opin Nephrol Hypertens 2001;10:183–7.
67. Kaplan JM, Kim SH, North KN, Rennke H, Correia LA, Tong HQ, et al. Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. Nat Genet 2000;24:251–6.
68. Honda K, Yamada T, Endo R, Ino Y, Gotoh M, Tsuda H, et al. Actinin-4, a novel actin-bundling protein associated with cell motility and cancer invasion [published erratum appears in J Cell Biol 1998 Oct 5;143(1):following 276]. J Cell Biol 1998;140:1383–93.
69. Kos CH, Le TC, Sinha S, Henderson JM, Kim SH, Sugimoto H, et al. Mice deficient in alpha-actinin-4 have severe glomerular disease. J Clin Invest 2003;111:1683–90.
70. Togawa A, Miyoshi J, Ishizaki H, Tanaka M, Takakura A, Nishioka H, et al. Progressive impairment of kidneys and reproductive organs in mice lacking Rho GDIalpha. Oncogene 1999;18:5373–80.
71. Savin V, Sharma R, Sharma M, McCarthy ET, Swan SK, Ellis E, et al. Circulating factor associated with increased glomerular permeability to albumin in reccurrent focal segmental glomerular sclerosis. N Engl J Med 1996;334:878–83.
72. Le Berre L, Godfrin Y, Gunther E, Buzelin F, Perretto S, Smit H, et al. Extrarenal effects on the pathogenesis and relapse of idiopathic nephrotic syndrome in Buffalo/Mna rats. J Clin Invest 2002;109:491–8.
73. Kriz W, Gretz N, Lemley KV. Progression of glomerular diseases: is the podocyte the culprit? Kidney Int 1998;54:687–97.
74. Kriz W. Progressive renal failure – inability of podocytes to replicate and the consequences for development of glomerulosclerosis. Nephrol Dial Transplant 1996;11:1738–42.
75. Steffes MW, Schmidt D, McCrery R, Basgen JM, Group ID. Glomerular cell number in normal subjects and in type 1 diabetic patients. Kidney Int 2001;59:2104–13.
76. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, et al. Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 1997;99:342–8.
77. Meyer TW, Bennett PH, Nelson RG. Podocyte number predicts long-term urinary albumin excretion in Pima Indians with Type II diabetes and microalbuminuria. Diabetologia 1999;42:1341–4.
78. Lemley KV, Lafayette RA, Safai M, Derby G, Blouch K, Squarer A, et al. Podocytopenia and disease severity in IgA nephropathy. Kidney Int 2002;61:1475–85.
79. Kim YH, Goyal M, Kurnit D, Wharram B, Wiggins J, Holzman L, et al. Podocyte depletion and glomerulosclerosis have a direct relationship in the PAN-treated rat. Kidney Int 2001;60:957–68.
80. Schiffer M, Bitzer M, Roberts IS, Kopp JB, ten Dijke P, Mundel P, et al. Apoptosis in podocytes induced by TGF-beta and Smad7. J Clin Invest 2001;108:807–16.