Podocyte injury and repair mechanisms

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INTRODUCTION

Podocytes are extremely ramified cells, covering with their primary and secondary (foot) processes the outer aspect of the glomerular basement membrane. It has been known for many years that ramifications from a podocyte intertwine with those from neighboring cells, and this arrangement has been recently confirmed by Tao *et al*. [1] who could describe differently labeled neighbor podocytes within glomeruli of the 'Confetti mouse'.

Podocytes have multiple functions in the glomerulus. They organize, mainly through secretion of vascular endothelial growth factor, the arrival and maturation of the glomerular endothelium during embryonic development; they secrete major components of the glomerular basement membrane; and, most importantly, they ensure proper glomerular filtration for the entire life of the organism, working in concert with the other components of the glomerular filtration barrier.

The complex structure of the podocyte, its level of differentiation, and the elaborated wrapping around the glomerular capillary have hampered for several years the possibility of obtaining accurate information on the physiological and pathological properties of this cell. Significant progress has been made recently, because of the increased ability to culture podocytes *in vitro*, the generation of more sophisticated animal models, and, in particular, as a result of the identification with genetic techniques of the molecules mutated in the most severe forms of podocyte disease. Genetic discoveries have been exceptionally important for two main reasons: first, they have allowed the precise diagnosis of several forms of proteinuric kidney diseases, which were generically labeled as steroid-resistant nephrotic syndrome; second, they have been the starting point for functional studies on the identified molecules,

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KEY POINTS

- Podocytes play a key role in the homeostasis of the glomerular filtration barrier.
- Research is unraveling the molecular pathways implicated in podocyte injury.
- Better knowledge of podocyte damage is rapidly leading to novel therapies.
- Targeted delivery of drugs to the podocyte can reduce drug dosage and unwanted side-effects.

leading to a better knowledge of podocyte functions.

Podocyte damage inevitably results in leakage of proteins from the glomerular filter and their loss in the urine. Insults causing podocyte injury are varied, from genetic mutations to inflammatory, toxic, metabolic, and hemodynamic changes that can occur primarily or secondarily within the kidney. The majority of these insults cause a typical modification of podocyte morphology, consisting of the flattening of the ramifications, named podocyte foot process effacement.

As recently described by Kriz *et al.* [2], foot process effacement seems to proceed in two phases. A first phase is characterized by a first-foot process retraction, with loss or displacement of the specialized adhesion between podocyte foot processes, the so-called slit diaphragm, which is replaced by occludens-like junctions (Fig. 1a) [3]. These changes seem rapidly reversible, as it can be observed in the protamine sulfate model after heparin injection, or with steroid treatment in human minimal change disease. In a second phase, more difficult to repair, foot processes completely retract and the glomerular basement membrane appears covered by a homogeneous cytoplasmic layer (Fig. 1b) because of prominent cytoskeletal rearrangement. Podocyte damage and foot process retraction leave behind denuded spaces of the glomerular basement membrane, ultimately leading to glomerular scarring if not properly repaired.

PODOCYTE INJURY CAUSED BY GENETIC CHANGES

The molecules implicated in genetically mediated podocyte damage can be grouped according to their location and function. Not surprisingly, the first uncovered mutations were of genes encoding for proteins located at the slit diaphragm, that is, NPHS1, NPHS2, NPHS3, CD2AP, and TRPC6.

Interestingly, recent studies on NPHS2, the gene-encoding podocin, have revealed additional information, which is relevant to genetic counseling and patient health because pathogenicity of an NPHS2-mutant allele seems to depend on the presence of a second transassociated mutation [4▪▪]. The authors showed that podocin undergoes altered heterodimerization and mislocalization only in the presence of both mutant alleles, with a final dominant-negative effect, whereas mutation of a single allele behaves as recessive.

Cytoskeletal-related genes (SMARCL1, ACTN4, MYH9, Myo1E, ARHGAP24, INF2) have also emerged as important determinants of nephrotic syndrome, confirming the profound association between podocyte structure and function. A recent addition to this group came with the identification of two deleterious mutations of ANLN, the gene encoding the actin-binding protein anillin in two

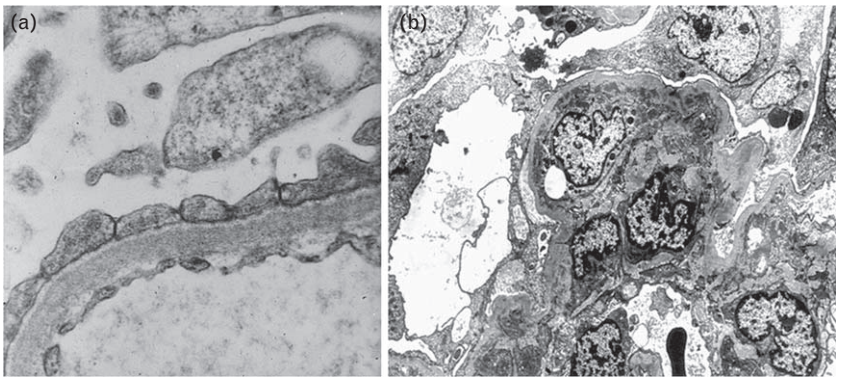

FIGURE 1. Podocyte foot process effacement. Transmission electron microscopy clearly illustrates the broadening of podocyte processes and replacement of the slit diaphragm with occludens-type junctions in a patient diagnosed with minimal change disease (a, ×10 000), and the complete podocyte foot process effacement in a patient affected by focal segmental glomerulosclerosis (b, ×2800). Adapted from [3].

families with autosomal dominant focal segmental glomerulosclerosis (FSGS). Anillin has been shown to interact with Rho GTPase, F-actin, and myosin II. When anillin is knocked down, active Rho (Rho-GTP), F-actin, and myosin II are consequently altered at the intercellular junctions [5].

The identification of mutations in organelle-related genes, mostly responsible for syndromic forms of nephrotic syndrome, served to drive attention on the relevance of mitochondrial (MTTL1, COQ6, COQ2, PDSS2) and lysosomal (SCARB2) functions in podocytes.

Cong *et al.* [6▪▪] identified a homozygous missense mutation in the TTC21B gene in seven families with FSGS and rapid progression to end-stage renal failure. TTC21B is a ciliary gene, previously found associated with nephronophthisis [7], and novel data now show that the TTC21B gene product intraflagellar transport protein 139 is present at the base of the primary cilium in immature podocytes from human fetal kidney and in an undifferentiated podocyte cell line, whereas it is located along microtubules in mature cells. Intraflagellar transport protein 139 knockdown in podocytes led to cilia defects, altered migration, and cytoskeletal changes. Transfection of knockout (KO) podocytes with the mutant protein partially rescued the phenotype, indicating a hypomorphic effect [6▪▪]. Interestingly, kidney tissue from patients carrying the mutation displayed thickening of the tubular basement membrane, which may account for tubular damage and progression to renal failure.

More recently, WDR73 mutations were identified in two families affected by Galloway–Mowat syndrome [8▪], a rare autosomal-recessive condition characterized by nephrotic syndrome associated with microcephaly and neurological impairment. The WDR73 product, a WD40-repeat-containing protein of previously unknown function, seems to be involved in the formation of spindle poles and microtubule asters during mitosis. In the kidney, podocyte expression is clearly observed during development, but it is lost in mature glomeruli, indirectly confirming the association with the mitotic cycle.

INFLAMMATORY, TOXIC, AND METABOLIC INJURY: THE LINK BETWEEN INFLAMMASOMES AND AUTOPHAGY

The large majority of glomerular diseases are characterized by deposition of immunoglobulins or complement components, or both of these, which initiate inflammatory pathways that lead to progressive glomerular and tubulointerstitial damage. Even in metabolic disorders, such as diabetic nephropathy, the role of inflammatory mechanisms is emerging as a prominent element in disease progression [9]. In recent years, the attention of researchers investigating podocyte injury during inflammatory and metabolic diseases has been attracted by two major pathways, that is, the nucleotide-oligomerization domain-like receptor 3 (NLRP3) inflammasome and autophagy.

The inflammasome is a group of multimeric protein complexes that consist of first, sensor molecules, the best studied of which is the pattern recognition receptor NLRP3, second, adaptor proteins, the most common being apoptosis-associated speck-like protein, and third, caspase 1. When NLRP3 is complexed with pro-caspase-1, it leads to the formation of active caspase-1, which cleaves prointerleukin 1β and prointerleukin 18 into their active forms [10].

Inflammasome formation can be induced either by exogenous molecules, such as those deriving from infective or toxic events, or by mislocalization of endogenous molecules, which occurs during cell damage, autoimmunity, and metabolic imbalances.

Proper activation of the inflammasome is an important first-line defense that belongs to innate immunity, but aberrant inflammasome activation has now been proven to contribute to the pathogenesis of numerous diseases, including autoimmune diseases, such as systemic lupus erythematosus [11].

As demonstrated by Zhang *et al.* [12], murine podocytes can express all the key components of the inflammasome (i.e. the NLRP3 receptor, the adaptor protein apoptosis-associated speck-like protein, and caspase 1), whose activation contributes to glomerulosclerosis in a model of hyperhomocysteinemia. Xia *et al.* [13] observed all inflammasome components and interleukin 1β production in glomeruli of wild-type mice with hyperhomocysteinemia, but not in those lacking NLRP3, and lack of inflammasome formation in these animals corresponded to lower glomerular damage, more preserved glomerular expression of nephrin and podocin, and lower proteinuria.

Shahzad *et al.* [14] observed inflammasome components and activation in endothelial cells and podocytes in in-vitro and in-vivo models of diabetes and in renal biopsies of diabetic nephropathy. Abolishing NLRP3 or caspase-1 expression selectively in bone marrow-derived cells failed to protect mice against diabetic nephropathy, and transplantation of wild-type bone marrow in NLRP3-KO diabetic animals did not increase glomerular damage. The authors also showed that administration of interleukin-1 receptor (IL-1R) antagonists prevented or even reversed diabetic nephropathy in mice. Activation of the NLRP3 inflammasome in

these diabetic models appeared to be due to mitochondrial reactive oxygen species because inhibiting mitochondrial reactive oxygen species production prevented glomerular inflammasome activation and nephropathy.

Autophagy is a conserved intracellular catabolic pathway and a key process for maintaining intracellular homeostasis [15]. Inflammatory responses have been shown to affect autophagy, but a clear understanding of the complex relationship between the immune system, autophagy, and glomerular diseases is still lacking.

Interestingly, a series of studies has found a mutual relationship between autophagy and the inflammasome, showing on one hand that autophagy negatively regulates inflammasome activation, but on the other hand that induction of autophagy depends on the presence of specific inflammasome sensors [16,17], and that autophagy plays a key role in biogenesis and secretion of interleukin 1β [18]. In addition, it has been shown that inflammasomes themselves are ultimately degraded by autophagosomes via the selective autophagic receptor protein 62 [19].

So far, most studies concerning glomerular diseases have demonstrated a protective role of autophagy. Healthy podocytes, as reported by Hartleben *et al.* [20], seem to exhibit a particularly high level of constitutive autophagy. These authors showed that podocyte-specific deletion of autophagy-related protein 5 makes the animals more susceptible to glomerular damage and with age causes the appearance of proteinuria and glomerular damage, with the accumulation of oxidized and ubiquitinated proteins and endoplasmic reticulum stress.

More recent works seem to confirm that podocytes need autophagy to maintain their functions. According to Zeng *et al.* [21], the glomeruli of patients with minimal change disease have more Beclin1-mediated autophagic activity than those with FSGS, and progression from minimal change to FSGS is accompanied by decreasing autophagy. Beclin1-KO mice, or animals treated with autophagy inhibitors, experience more severe damage in the context of puromycin aminonucleoside-induced podocyte injury, whereas induction of autophagy by the mTOR inhibitor rapamycin reduces podocyte damage.

Kawakami *et al.* [22] induced mutations of the autophagy genes autophagy-related protein 5 or autophagy-related protein 7 during mouse nephrogenesis. This was enough to cause a progressive podocyte and tubular disease that reached renal failure by 6 months. Both podocytes and tubular cells displayed vacuolization, abnormal mitochondria, and evidence of endoplasmic reticulum stress, which were detectable biochemically and by electron microscopy before renal lesions could be observed by light microscopy.

PODOCYTE REPAIR

Improved knowledge of the molecular mechanisms occurring during podocyte injury rapidly leads to the identification of numerous therapeutic targets potentially useful to achieve podocyte repair, and translation of experimental data into clinical practice will constitute a major challenge in the near future. Timing of any therapeutic intervention constitutes a relevant issue, particularly considering that in humans podocyte damage remains silent until proteinuria is detected.

It is worth noting that a number of drugs already in use for the treatment of glomerular diseases have shown the ability to directly act on the podocyte because of podocyte expression of drug receptors or enzymatic targets [23–25]. Precise podocyte delivery of novel and old drugs can now be envisaged as a result of major developments in nanotechnology and nanomedicine, taking into account that the use of nanocarriers and engineered biomolecules for targeted therapies has already entered human application in other fields of medicine [26,27]. Recently, size-controlled inorganic nanomaterials, such as gold nanoparticles and quantum dots, have been investigated *in vitro* and *in vivo* for glomerular [28] and podocyte [29] targeting.

Specific cell delivery of drugs would have obvious advantages in terms of dose reduction, improvement of the drug half-life, and avoidance of side-effects, which could be significant in cases where a precise molecular target is relevant for other cell types. This concept has been proved by the appearance of glomerular injury and proteinuria in patients affected by cancer and treated with humanized antibodies against vascular endothelial growth factor [30].

As another example, it has been shown that amelioration of podocyte damage can be reached experimentally by acting on the Notch pathway, either by blocking Notch1, as recently reviewed by Kato and Susztak [31], or by activating Notch2, as described by Tanaka *et al.* [32]. Several compounds have been produced that are influencing the Notch pathways and human trials are ongoing in the field of oncology (https://clinicaltrials.gov). However, these interventions in the kidney will necessitate specific cell delivery, as it has been found that glomeruli display a different Notch expression and pathway activation as compared with the tubulointerstitium [33].

One of the most attractive possibilities for driving podocyte repair, action on the integrins differentially expressed or activated/inactivated during podocyte damage, could potentially result in amelioration of cell attachment to the glomerular basement membrane and reequilibration of cell motility [34]. Abatacept, a drug recently utilized in steroid-resistant nephrotic syndrome, seems to act on podocyte de-novo expression of the costimulatory molecule B7-1, which in turn results in changes of integrin beta1 activation and overall amelioration of podocyte adhesion and stability [35]. Interestingly, integrin beta 1 activation can also result from activated Rap1, a small G protein with 53% amino acid identity to Ras [36]. Reduced Rap1 activation, as it occurs during human and experimental podocyte damage, can be due to increased activity of Rap1GAP, a GTPase-activating protein that accelerates hydrolysis of bound GTP to GDP, blocking the activity of small G proteins [37].

Finally, numerous studies address the possibility of exploiting the regenerative potential of podocytes. Among different podocyte progenitors [38–42], most studies have focused on parietal epithelial cells, that is the cells forming the Bowman's capsule. At least a subpopulation of parietal cells has demonstrated the ability to become podocytes *in vitro*, and lineage tracing studies have shown the participation of parietal epithelial cells in the development of the glomerular tuft [43].

However, the actual possibility that parietal epithelial cells contribute to repairing podocyte damage is still controversial and different results have been obtained, most likely because of the different experimental models utilized, the timing of analysis, and the severity of disease [44,45,46▪,47▪]. Instead, there seems to be more consensus on the participation of parietal epithelial cells in glomerulosclerosis and extracapillary proliferation [48–51].

The use of mesenchymal stem cells has also been proposed to repair podocyte injury. Mesenchymal stem cells seem not to repopulate the glomerulus, but rather to act by secreting immunomodulatory factors that can help disease resolution [52].

An additional, as yet under-developed, possibility is the derivation of podocytes from induced pluripotent stem cells [53]. This technology has several interesting research and therapeutic implications because of the possibility of obtaining induced pluripotent stem cells from patients' accessible cells, such as fibroblasts or cells from the urinary sediment.

CONCLUSION

In summary, research is making rapid progress in uncovering the molecular pathways implicated in different types of podocyte injury.

These results offer multiple possibilities for the better treatment of podocyte damage, including possible regeneration, rising the hope of abating the number of patients reaching terminal renal failure.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Tao J, Polumbo C, Reidy K, *et al.* A multicolor podocyte reporter highlights heterogeneous podocyte changes in focal segmental glomerulosclerosis. Kidney Int 2014; 85:972–980.
2. Kriz W, Shirato I, Nagata M, *et al.* The podocyte's response to stress: the enigma of foot process effacement. Am J Physiol Renal Physiol 2013; 304:F333–F347.
3. Ferrario F, Rastaldi MP. Histopathological atlas of renal diseases. http://www.fondazionedamico.org/biopsiarenale_atlas/prim/mc-gsf/mc.htm [Accessed 25 February 2015].
4. ▪▪ Tory K, Menyhárd DK, Woerner S, *et al.* Mutation-dependent recessive inheritance of NPHS2-associated steroid-resistant nephrotic syndrome. Nat Genet 2014; 46:299–304.

Results are relevant to diagnosis and genetic counseling.

5. Gbadegesin RA, Hall G, Adeyemo A, *et al.* Mutations in the gene that encodes the F-actin binding protein anillin cause FSGS. J Am Soc Nephrol 2014; 25:1991–2002.
6. ▪▪ Cong EH, Bizet AA, Boyer O, *et al.* A homozygous missense mutation in the ciliary gene TTC21B causes familial FSGS. J Am Soc Nephrol 2014; 25:2435–2443.

First evidence for a ciliary gene implicated in FSGS.

7. Otto EA, Ramaswami G, Janssen S, *et al.* Mutation analysis of 18 nephronophthisis associated ciliopathy disease genes using a DNA pooling and next generation sequencing strategy. J Med Genet 2011; 48:105–116.
8. ▪ Colin E, Huynh Cong E, Mollet G, *et al.* Loss-of-function mutations in WDR73 are responsible for microcephaly and steroid-resistant nephrotic syndrome: Galloway–Mowat syndrome. Am J Hum Genet 2014; 95:637–648.

The first gene causative of Galloway–Mowat syndrome has been identified.

9. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest 2014; 124:2333–2340.
10. Davis BK, Wen H, Ting JP. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 2011; 29:707–735.
11. Shin MS, Kang Y, Lee N, *et al.* U1-small nuclear ribonucleoprotein activates the NLRP3 inflammasome in human monocytes. J Immunol 2012; 188:4769–4775.
12. Zhang C, Boini KM, Xia M, *et al.* Activation of Nod-like receptor protein 3 inflammasomes turns on podocyte injury and glomerular sclerosis in hyperhomocysteinemia. Hypertension 2012; 60:154–162.
13. Xia M, Conley SM, Li G, *et al.* Inhibition of hyperhomocysteinemia-induced inflammasome activation and glomerular sclerosis by NLRP3 gene deletion. Cell Physiol Biochem 2014; 34:829–841.
14. Shahzad K, Bock F, Dong W, *et al.* Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy. Kidney Int 2015; 87:74–84.
15. Kelekar A. Autophagy. Ann N Y Acad Sci 2005; 1066:259–271.
16. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature 2011; 469:323–335.
17. Deretic V. Autophagy: an emerging immunological paradigm. J Immunol 2012; 189:15–20.

18. Dupont N, Jiang S, Pilli M, *et al.* Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1β. EMBO J 2011; 30:4701–4711.
19. Shi CS, Shenderov K, Huang NN, *et al.* Activation of autophagy by inflammatory signals limits IL-1β production by targeting ubiquitinated inflammasomes for destruction. Nat Immunol 2012; 13:255–263.
20. Hartleben B, Gödel M, Meyer-Schwesinger C, *et al.* Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. J Clin Invest 2010; 120:1084–1096.
21. Zeng C, Fan Y, Wu J, *et al.* Podocyte autophagic activity plays a protective role in renal injury and delays the progression of podocytopathies. J Pathol 2014; 234:203–213.
22. Kawakami T, Gomez IG, Ren S, *et al.* Deficient autophagy results in mitochondrial dysfunction and FSGS. J Am Soc Nephrol 2014; doi: 10.1681/ASN.2013111202. [Epub ahead of print]
23. Xing CY, Saleem MA, Coward RJ, *et al.* Direct effects of dexamethasone on human podocytes. Kidney Int 2006; 70:1038–1045.
24. Faul C, Donnelly M, Merscher-Gomez S, *et al.* The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med 2008; 14:931–938.
25. Fornoni A, Sageshima J, Wei C, *et al.* Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med 2011; 3:85ra46.
26. Rink JS, Plebanek MP, Tripathy S, Thaxton CS. Update on current and potential nanoparticle cancer therapies. Curr Opin Oncol 2013; 25:646–651.
27. Aditya NP, Vathsala PG, Vieira V, *et al.* Advances in nanomedicines for malaria treatment. Adv Colloid Interface Sci 2013; 201–202:1–17.
28. Choi CH, Zuckerman JE, Webster P, Davis ME. Targeting kidney mesangium by nanoparticles of defined size. Proc Natl Acad Sci U S A 2011; 108:6656–6661.
29. Pollinger K, Hennig R, Breunig M, *et al.* Kidney podocytes as specific targets for cyclo(RGDfC)-modified nanoparticles. Small 2012; 8:3368–3375.
30. Eremina V, Jefferson JA, Kowalewska J, *et al.* VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008; 358:1129–1136.
31. Kato H, Susztak K. Repair problems in podocytes: Wnt, Notch, and glomerulosclerosis. Semin Nephrol 2012; 32:350–356.
32. Tanaka E, Asanuma K, Kim E, *et al.* Notch2 activation ameliorates nephrosis. Nat Commun 2014; 5:3296.
33. Sanchez-Niño MD, Ortiz A. Notch3 and kidney injury: never two without three. J Pathol 2012; 228:266–273.
34. Lennon R, Randles MJ, Humphries MJ. The importance of podocyte adhesion for a healthy glomerulus. Front Endocrinol (Lausanne) 2014; 5:160.
35. Yu CC, Fornoni A, Weins A, *et al.* Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2013; 369:2416–2423.
36. Bos JL, de Rooij J, Reedquist KA. Rap1 signalling: adhering to new models. Nat Rev Mol Cell Biol 2001; 2:369–377.
37. Potla U, Ni J, Vadaparampil J, *et al.* Podocyte-specific RAP1GAP expression contributes to focal segmental glomerulosclerosis-associated glomerular injury. J Clin Invest 2014; 124:1757–1769.
38. Becker JU, Hoerning A, Schmid KW, Hoyer PF. Immigrating progenitor cells contribute to human podocyte turnover. Kidney Int 2007; 72:1468–1473.
39. Nishinakamura R. Stem cells in the embryonic kidney. Kidney Int 2008; 73:913–917.
40. Ronconi E, Sagrinati C, Angelotti ML, *et al.* Regeneration of glomerular podocytes by human renal progenitors. J Am Soc Nephrol 2009; 20:322–332.
41. Da Sacco S, Lemley KV, Sedrakyan S, *et al.* A novel source of cultured podocytes. PLoS One 2013; 8:e81812.
42. Pippin JW, Sparks MA, Glenn ST, *et al.* Cells of renin lineage are progenitors of podocytes and parietal epithelial cells in experimental glomerular disease. Am J Pathol 2013; 183:542–557.
43. Appel D, Kershaw DB, Smeets B, *et al.* Recruitment of podocytes from glomerular parietal epithelial cells. J Am Soc Nephrol 2009; 20:333–343.
44. Zhang J, Pippin JW, Krofft RD, *et al.* Podocyte repopulation by renal progenitor cells following glucocorticoids treatment in experimental FSGS. Am J Physiol Renal Physiol 2013; 304:F1375–F1389.
45. Hakroush S, Cebulla A, Schaldecker T, *et al.* Extensive podocyte loss triggers a rapid parietal epithelial cell response. J Am Soc Nephrol 2014; 25:927–938.
46. ■ Berger K, Schulte K, Boor P, *et al.* The regenerative potential of parietal epithelial cells in adult mice. J Am Soc Nephrol 2014; 25:693–705.
The manuscript describes limited podocyte regeneration by parietal cells.
47. ■ Wanner N, Hartleben B, Herbach N, *et al.* Unraveling the role of podocyte turnover in glomerular aging and injury. J Am Soc Nephrol 2014; 25:707–716.
The manuscript describes limited podocyte regeneration by parietal cells.
48. Smeets B, Kuppe C, Sicking EM, *et al.* Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. J Am Soc Nephrol 2011; 22:1262–1274.
49. Sicking EM, Fuss A, Uhlig S, *et al.* Subtotal ablation of parietal epithelial cells induces crescent formation. J Am Soc Nephrol 2012; 23:629–640.
50. Sakamoto K, Ueno T, Kobayashi N, *et al.* The direction and role of phenotypic transition between podocytes and parietal epithelial cells in focal segmental glomerulosclerosis. Am J Physiol Renal Physiol 2014; 306:F98–F104.
51. Gaut JP, Hoshi M, Jain S, Liapis H. Claudin 1 and nephrin label cellular crescents in diabetic glomerulosclerosis. Hum Pathol 2014; 45:628–635.
52. Zoja C, Garcia PB, Rota C, *et al.* Mesenchymal stem cell therapy promotes renal repair by limiting glomerular podocyte and progenitor cell dysfunction in adriamycin-induced nephropathy. Am J Physiol Renal Physiol 2012; 303:F1370–F1381.
53. Song B, Smink AM, Jones CV, *et al.* The directed differentiation of human iPS cells into kidney podocytes. PLoS One 2012; 7:e46453.