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Glomerular Epithelial Stem Cells: The Good, The Bad, and The Ugly

Laura Lasagni* and Paola Romagnani*†

*Excellence Centre for Research, Transfer and High Education for the development of De Novo Therapies (DENOTHE), University of Florence, Florence, Italy; and †Pediatric Nephrology Unit, Meyer University Hospital, Florence, Italy

ABSTRACT

Global glomerulosclerosis with loss of podocytes in humans is typical of end-stage renal pathology. Although mature podocytes are highly differentiated and nondividing, converging evidence from experimental and clinical data suggests adult stem cells within Bowman's capsule can rescue some of this loss. Glomerular epithelial stem cells generate podocytes during kidney growth and regenerate podocytes after injury, thus explaining why various glomerular disorders undergo remission occasionally. This regenerative process, however, is often inadequate because of inefficient proliferative responses by glomerular epithelial stem cells with aging or in the setting of focal segmental glomerulosclerosis. Alternatively, an excessive proliferative response by glomerular epithelial stem cells after podocyte injury can generate new lesions such as extracapillary crescentic glomerulonephritis, collapsing glomerulopathy and tip lesions. Better understanding of the mechanisms that regulate growth and differentiation of glomerular epithelial stem cells may provide new clues for prevention and treatment of glomerulosclerosis.

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Global glomerulosclerosis in humans accompanies most progressive renal pathology. Although primary injury to each of the somatic cell types in the glomerular tuft associates with some form of glomerular disease, injury to endothelial and mesangial cells repair by proliferation of adjacent cells.[1,2] By contrast, podocytes are highly differentiated, neuron-like cells that cannot divide,[1,2] which explains why podocyte injury is a key driver of focal or global glomerulosclerosis.[3] Indeed, a large body of evidence from experimental models suggests loss of podocytes over a certain threshold induces glomerulosclerosis.[2–7] Podocyte number is also reduced in proportion to the severity of injury and degree of proteinuria, and predicts progression in patients with diabetic nephropathy, IgA nephropathy, and focal segmental glomerulosclerosis (FSGS).[1,8–13] Finally, mutations that produce a glomerulosclerosis occur exclusively among genes expressed by the podocyte.[14–16]

Interestingly, depletion of highly specialized cells with limited capacity to divide is a common pathway driving many types of organ failure.[17–20] In other adult organs, loss of highly specialized cells during injury can be replaced by resident stem cells.[21,22] For example, neuronal cell depletion after ischemic injury generates brain dysfunction, but neuronal stem cells in the adult brain also drive replacement of lost neurons with some functional recovery.[22] Accordingly, severe podocyte loss and glomerulosclerosis can be rescued occasionally by replacement.[23–27] Data from experimental models also demonstrate that regression of glomerulosclerosis can occur by increasing podocyte number.[23–25] Because resident podocytes do not divide, this suggests that new podocytes derive by regeneration. Regression of renal disease with remodeling of glomerular architecture is observed in pancreatic transplant patients with type 1 diabetes after 10 years of normoglycemia[26] and in patients treated chronically with angiotensin-converting enzyme inhibitors.[23–27] Taken together, these results imply there are stem cells in adult glomeruli with the potential to regenerate podocytes.

THE GOOD: GLOMERULAR EPITHELIAL STEM CELLS REGENERATE PODOCYTES

Stem cells are functionally defined by their ability to self-renew and differentiate into cell lineages reflecting their tissue of origin.[21] The ability to self-renew stem cells is maintained by a process called symmetric division, where new daughter cells maintain all the functional and phenotypic properties of stem cells.[21] However, once activated, stem cells can also regenerate by asymmetric division, producing a daughter stem cell and a com-

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Correspondence: Dr. Paola Romagnani, Department of Clinical Pathophysiology, Nephrology Section, University of Florence, Viale Pieraccini 6, 50139 Firenze, Italy. Phone: +39554271356; Fax: +39554271357; E-mail: p.romagnani@dfc.unifi.it

mitted progenitor.[21] In their normal environment, committed progenitors retain the capacity to divide and differentiate toward a particular lineage.

Recently, we provided the first evidence that adult human glomeruli contain a hierarchical population of stem and committed progenitor cells.[28–33] These resident stem and progenitor cells localize within the Bowman's capsule and are identified by the presence of both CD24 and CD133, two surface molecules that are shared by different types of human adult stem cells.[34,35] $CD24^+$, $CD133^+$ cells localize at the urinary pole of Bowman's capsule and exhibit self-renewal properties and also the potential to differentiate into podocytes or proximal tubular cells (Figure 1).[33] Clonal analyses demonstrate this subset of parietal epithelial cells represent multipotent epithelial stem cells and not simply a mixture of unipotent progenitors.[33] This feature was demonstrated by first culturing progeny derived from single $CD24^+$, $CD133^+$ cells and then transplanting them into SCID mice with focal segmental glomerulosclerosis (FSGS).[33]

$CD24^+$, $CD133^+$ stem cells follow a phenotypical and functional hierarchy to generate a population of podocyte-committed progenitors between the urinary and the vascular pole of Bowman's capsule, expressing both stem cells and podocyte markers (Figure 1). These progenitors differentiate only toward the podocyte lineage and lack the properties of self-renewal.[33] Previous studies show the existence of transitional cells exhibiting a mixed phenotype between parietal epithelial cells and neo-podocytes in proximity of the vascular stalk of the glomerulus.[36,37] Podocyte-committed progenitors proliferate and differentiate into cells that loose stem cell markers and acquire high levels of podocyte-specific markers as they progressively migrate toward the vascular stalk of the Bowman's capsule (Figure 1).[33] These findings in humans were also confirmed in parallel studies performed in rodents. Indeed, using genetic tagging of parietal epithelial cells, Appel *et al.*[38] demonstrated that such cells proliferate and differentiate along the urinary space and move to the vascular stalk generating neo-podocytes (Figure 1).[38] Genetic labeling also supports the notion that this parietal epithelial cell population regenerates itself.[38] Thus, parietal epithelial cells have the ability not only to generate differentiated podocytes but also to self-renew, which further demonstrates they represent stem cells. A continuous generation of novel podocytes occurs as the kidney grows,[38] and might also occur during enlargement of a contralateral kidney after uninephrectomy.

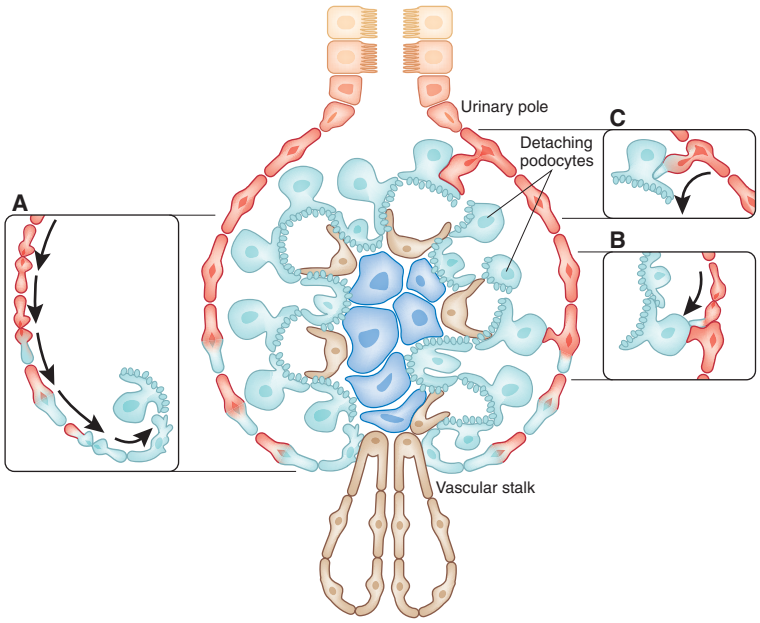

Figure 1. The good: Glomerular epithelial stem cells regenerate podocytes. Glomerular epithelial stem cells (red) are localized at the urinary pole. A transitional cell population (podocyte progenitors, red/light blue) displays features of either glomerular epithelial stem cells or podocytes (light blue) and localize between the urinary pole and the vascular stalk. Cells that express only podocyte markers and the phenotypic features of differentiated podocytes localize at the vascular stalk of the glomerulus or within the glomerular tuft (light blue). Proposed mechanisms of podocyte regeneration are depicted in more detail in (A), (B), and (C). (A) Glomerular epithelial stem cells can self-renew and also generate novel podocytes by progressively proliferating and differentiating toward the vascular stalk. This occurs as the kidney grows, during childhood and adolescence, and might also occur after an injury, which allows for a slow generation of novel podocytes, such as after uninephrectomy. (B and C) In glomerular disorders characterized by severe podocyte death or detachment, glomerular epithelial stem cells generate cell bridges between the Bowman's capsule and the glomerular tuft, which may allow a quick replacement of lost podocytes. (B) Cell bridges may provide a slide for the migration, proliferation, and differentiation of an adjacent progenitor and a quick replacement of lost podocytes. (C) Bridging parietal epithelial cells might also acquire podocyte markers after injury and directly replace the lost podocytes. The directions of migration, proliferation, and differentiation of glomerular epithelial stem cells to regenerate lost podocytes are indicated by the arrows.

However, in glomerular disorders characterized by acute or severe podocyte loss, regeneration may require other pathways that allow faster replacement of injured podocytes. Indeed, the possibility that parietal epithelial cells also migrate from Bowman's capsule to the capillary tuft in regions different than the vascular pole is suggested by adhesions and also bridges representing new migratory tracks between Bowman's capsule and the tuft (Figure 1).[25,39] Interestingly, a recent study using genetic tagging of parietal epithelial cells demonstrates that bridges between Bowman's capsule and the glomerular tuft in experimental models of glomerular disorders are exclusively generated by parietal epithelial cells.[40] These bridges provide a pathway for the migration and differentia-

tion of an adjacent progenitor and a quick replacement of lost podocytes (Figure 1B), or alternatively, bridging parietal epithelial cells may acquire podocyte markers after injury[41] and directly replace lost podocytes (Figure 1C). Accordingly, generation of bridges by parietal epithelial cells to replace lost podocytes has also been recently reported using *in vivo* multiphoton microscopy in rat models of PAN nephritis.[42] In summary, a large body of evidence indicates the Bowman's capsule of adult kidneys contains a population of glomerular epithelial stem cells, which replace lost podocytes through multiple mechanisms of glomerular regeneration.

THE BAD: LIMITS AND DEFAULTS IN THE REGENERATIVE POTENTIAL OF GLOMERULAR EPITHELIAL STEM CELLS

Several studies indicate, as already reported for other types of adult stem cells,[20,21,43] that the regenerative capacity of glomerular epithelial stem cells has limits.[29,38,44,45] Wiggins and co-workers[1,3] find that repair of podocytes occurs when <20% of podocytes are lost; 20 to 40% podocyte loss results in a scarring response and >60% podocyte loss produces globally sclerotic and nonfiltering glomeruli. The amount of podocyte injury seems greatly influenced by the regenerative capacity of glomerular epithelial stem cells, and glomerulosclerosis leading to ESRD may occur in those glomerular disorders where the amount of podocyte injury exceeds the possibility of regeneration (Figure 2).[24,26] In addition, glomerular epithelial stem cells display a different regenerative potential at distinct stages of life,[38] exhibiting the highest regenerative potential through adolescence,[38] which might explain why glomerular disorders have a better prognosis during childhood whereas FSGS is more frequent at an older age (Figure 2).[1]

This observation also provides a possible explanation for the progressive increase in prevalence of global glomerulosclerosis with aging, which may be related to an exhaustion of the self-renewal potential of glomerular epithelial stem cells. Indeed, reduced potential for self-renewal with aging is described in other adult stem cells.[46–50] Accumulated DNA damage and loss of DNA repair may be one of the mechanisms underlying age-dependent stem cell decline.[47] However, the most important modulator of the regenerative potential of stem cells is likely to be the surrounding environment.[48–50] After birth, adult stem cells reside in a specialized microenvironment called a "niche," which regulates the delicate balance between self-renewal and differentiation.[21,48–52]

The localization of glomerular epithelial stem cells at the urinary pole of the Bowman's capsule suggests that the adult glomerulus contains such a stem cell niche. This hypothesis is supported by the observation that embryonic stem cells, after commitment toward renal lineages, migrate to the urinary pole of Bowman's capsule after injection into developing kidneys[53]—a selective property of stem cell niches.[21,48–52] Previous studies also demonstrate that factors present in young niche environments restore proliferative and regenerative capacity of aged stem cells in the niches of other adult tissues.[50]

Accordingly, very recent data finds that the regenerative potential of glomerular epithelial stem cells is enhanced or inhibited by different culture conditions.[54] More importantly, injection of glomerular epithelial stem cells under the contralateral kidney capsule of unilaterally nephrectomized mice generate novel renal tissue, including neo-glomerular and tubular structures, a finding that is not observed after injection under the capsule of normal kidneys.[54] This latter finding suggests the regenerative potential of glomerular epithelial stem cells is strictly dependent on the surrounding environment and the underlying process of kidney growth generates favorable conditions for regeneration.[38,54] Although a recent study describes the phenotype of glomerular epithelial

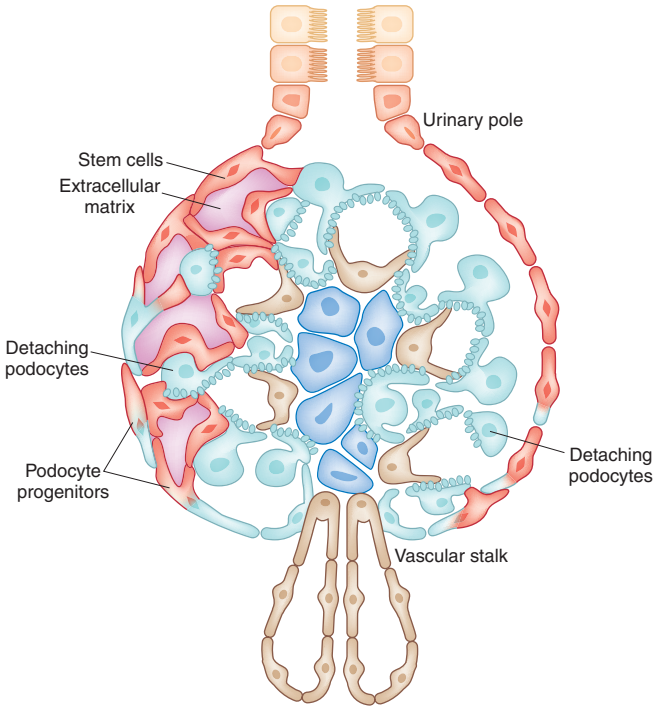

Figure 2. The bad: Limits and defaults of the regenerative potential of glomerular epithelial stem cells. Age, genetic alterations, and environmental factors limit the regenerative response of glomerular epithelial stem cells (red), thus impairing podocyte (light blue) replacement when the amount of injured cells is extensive. If regeneration is impaired, podocyte loss typically results in the deposition of extracellular matrix (pink), which can be produced by glomerular epithelial stem cells in response to TGF-β that is secreted by injured podocytes.

stem cells,[55] we still have little information about which other cells support their growth and differentiation and what paracrine factors maintain their function and number. Thus, further experiments are necessary to pinpoint this relationship and how it changes during progressive glomerulosclerosis or aging.

THE UGLY: DYSREGULATED GLOMERULAR EPITHELIAL STEM CELLS CREATE THEIR OWN LESIONS

It is widely recognized that disruption in the regulated balance between self-renewal and differentiation of stem cells not only impairs regenerative mechanisms but also can even create new problems.[48,52] For example, myeloproliferative diseases arise as a result of aberrant proliferation of hematopoietic stem cells,[56,57] whereas a number of hematopoietic stem cells are reduced in aplastic anemia, resulting in fatty replacement of bone marrow with pancytopenia.[58] These stem cells–related disorders are generated by intrinsic genetic alterations or by alterations of the surrounding environment.[56–58]

In the glomerulus, the response to podocyte injury may cause aberrant epithelial cell proliferation, the formation of hypercellular lesions, and the obliteration of Bowman's space, as seen in collapsing glomerulopathy or crescentic glomerulonephritis.[59–63] Until now, theories explaining the origin of aberrant epithelial cells in collapsing glomerulopathy and crescentic glomerulonephritis have been controversial.[59–69] One possibility is these cells are exclusively of parietal epithelial origin,[59–64] whereas others suggest some dedifferentiated podocytes acquire markers of parietal epithelial cells.[65–69]

After the identification of a population of glomerular epithelial stem cells along Bowman's capsule that generate new podocytes, we have explored the possibility that hyperplastic epithelial cells in crescentic glomerulonephritis or collapsing glomerulopathy might result from an aberrant proliferative response of these stem cells. This would easily explain the presence in these lesions of cells with an intermediate phenotype between parietal epithelial cells and podocytes.[59–69] Accordingly, the majority of cells present in the hyperplastic lesions of patients with collapsing glomerulopathy or crescentic glomerulonephritis exhibit the glomerular epithelial stem cell markers, CD133 and CD24, with or without co-expression of podocyte markers.[70] Therefore, we suggest that glomerular hyperplastic lesions are generated by stem/renal progenitor cells from Bowman's capsule at different stages of differentiation toward mature podocytes (Figure 3A).[70]

Additional confirmation of this hypothesis comes from lineage-tracing experiments performed in transgenic mice with genetically labeled parietal epithelial cells in the nephrotoxic nephritis model of crescentic glomerulonephritis and also the Thy-1.1 transgenic mouse model of collapsing glomerulopathy.[40] In both models, genetically labeled parietal epithelia constitute the majority of cells that compose early extracapillary proliferative lesions and almost all of the proliferating cells.[40] Interestingly, Le Hir *et al.* suggest the development of the crescent is initiated by cell bridges that are formed between the tuft and Bowman's capsule.[71] Because lineage-tracing experiments demonstrate that bridging between the Bowman's capsule and the tuft are generated by parietal epithelial cells,[40] we hypothesize that after massive

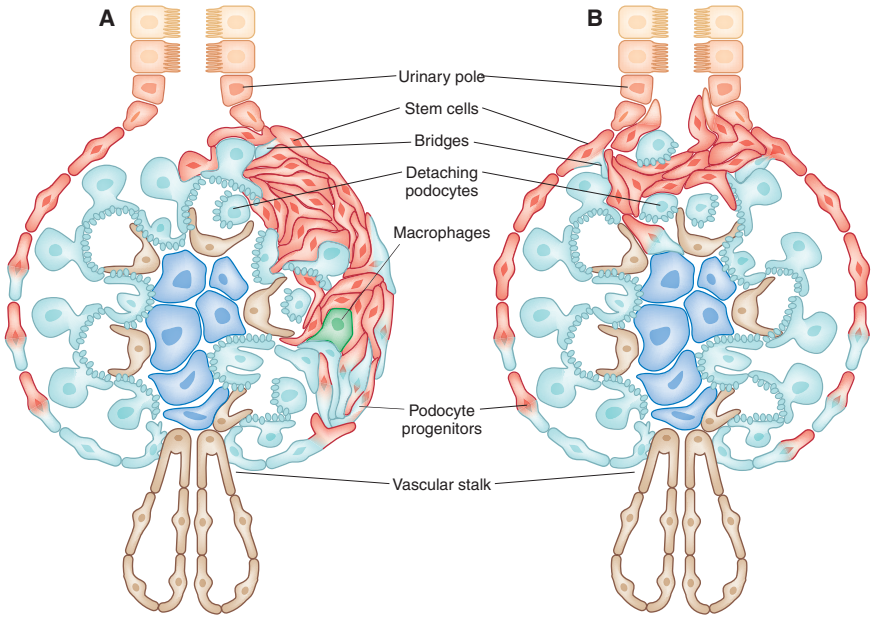

Figure 3. The ugly: Dysregulated glomerular epithelial stem cells create their own lesions. Aberrant proliferation of glomerular epithelial stem cells can generate hyperplastic lesions. (A) After massive podocyte injury, glomerular epithelial stem cells (red) generate cell bridges with the glomerular tuft in several areas of the glomerulus to quickly replace lost podocytes (light blue). However, numerous areas of podocyte injury distort glomerular structural integrity, thus altering the polarity of glomerular epithelial stem cell division and initiating their abnormal proliferation and the development of extracapillary hyperplastic lesions as well as crescents. Macrophages (green) can also be included within the lesions. Similar processes might occur in crescentic glomerulonephritis and collapsing glomerulopathy. (B) Replacement of podocytes under physiologic conditions follows a gradient, with neo-podocytes progressively added at the vascular stalk. Thus, the tip podocytes represent the "oldest" podocytes of the glomerular tuft, which suggests they might be more susceptible to injury related to heavy proteinuria. Glomerular epithelial stem cells may also proliferate and migrate from the urinary pole of the Bowman's capsule toward the tuft in an attempt to replace the podocytes lost in response to heavy proteinuria, and generate the tip lesion.

podocyte injury, glomerular epithelial stem cells generate cell bridges with the glomerular tuft in several areas of the glomerulus to quickly replace lost podocytes (Figure 3A).

Numerous areas of podocyte injury along with glomerular epithelial stem cells proliferation heavily distort glomerular architecture, thus altering the polarity of stem cells division. Polarized proliferation is a critical determinant of correct stem cell differentiation,[48–52] and this might explain why disruption in the polarity of glomerular epithelial stem cells initiates abnormal proliferation and the development of hyperplastic glomerular lesions impairing recovery (Figure 3A). Interestingly, both crescentic glomerulonephritis and collapsing glomerulopathy are characterized by death of numerous podocytes over a short time interval and by an aberrant proliferation of glomerular epithelial stem cells, which suggests they might not be pathogenically distinct but rather two faces of the same disorder.[72] That is, crescentic glomerulonephritis presents with podocyte damage in an inflammatory environment characterized by nephritic features, whereas collapsing glomerulopathy often presents with nephrotic features.[62,63,72,73]

Although epithelial cell proliferation is most characteristic and prominent in crescentic glomerulonephritis or collapsing glomerulopathy, some epithelial cell proliferation is also observed in histopathologic lesions typically found in other podocytopathies, such as the tip-lesion.[62] Interestingly, we recently demonstrated that in the tip lesion, as well as in those FSGS which are characterized by mild levels of hyperplasia, glomerular epithelial stem cells are the main constituents of the proliferative lesion.[70] This raises the question of how distinct pathogenic factors initiate abnormal regenerative processes.

FSGS is induced after a 40 to 60% podocyte loss.[1,3] However, in the face of massive podocyte injury in this disorder, hyperplastic glomerular lesions generated by glomerular epithelial stem cells are usually mild.[61] This suggests that FSGS might be the consequence of insufficient proliferation of glomerular epithelial stem cells, which impairs the correct replacement of injured podocytes and defaults to alternative replacement with extracellular matrix (Figure 2).[70] Interestingly, when glomerular epithelial stem cells are exposed to TGF-β secreted by podocytes exposed to proteinuria,[74] they also produce and deposit higher amounts of extracellular matrix.[70] In addition, the regenerative potential of glomerular epithelial stem cells is reduced in aging,[38] when FSGS is more frequent (Figure 2).[1,61]

Other reasons underlying the different response of glomerular epithelial stem cells to massive podocyte injury in various glomerulonephridities are currently unknown, but might be related to the type of injury or to the different genetic backgrounds of patients. Accordingly, a recent study demonstrates that podocyte damage leads to glomerular injury with a complete histologic pattern of collapsing glomerulopathy related to high parietal epithelial cell proliferation in mice with null alleles for the cell cycle inhibitor, *p21*, compared with segmental lesions and mild intraglomerular proliferation in wild-type mice.[75]

Finally, glomerular epithelial stem cells are also the main constituents of the tip lesion.[70] Interestingly, the tip lesion is described in several proteinuric conditions, including FSGS, membranous nephropathy,[76] postinfectious glomerulonephritis,[77] and diabetic nephropathy.[78] Because replacement of podocytes under physiologic conditions follows a gradient, with neo-podocytes progressively added from the vascular stalk, the tip podocytes likely represent the "oldest" podocytes in the glomerular tuft, as already suggested.[38] This should make the tip podocytes more susceptible to injury and thus suggests they might be the first to die in response to heavy proteinuria (Figure 3B). On this basis, Haas and Yousefzadeh[79] argue that the tip lesion is a response to prolonged heavy proteinuria.

Consistently, experimental evidence in *in vitro* and *in vivo* models of disease documents that exposure of podocytes to excessive amounts of plasma proteins promotes podocyte dysfunction and injury followed by tuft adhesion and sclerosis.[75,80] Thus, glomerular epithelial stem cells may proliferate and migrate from the urinary pole of the Bowman's capsule toward the tuft in an attempt to replace the podocytes lost in response to heavy proteinuria, generating the tip lesion (Figure 3B). Taken together, the results of these recent studies suggest the clinicopathologic features of different glomerular disorders more likely represent distinct patterns of injury or repair rather than diseases.

CONCLUSIONS

Podocyte loss is a central determinant of progression to glomerulosclerosis.[1,3–16] Podocytes cannot divide,[1,2] but regression of glomerulosclerosis is possible, as indicated by experimental models and also clinical evidence.[24–28] The discovery that a population of glomerular epithelial stem cells represent a potential source for podocyte regeneration establishes an entirely novel view that changes the way we think of normal renal cell biology or pathophysiology (Figure 1).[29–33,38,39] Indeed, the first main outcome of the discovery of glomerular epithelial stem cells is that regeneration or the promotion of functional repair after glomerular injury, and even prevention or treatment of glomerulosclerosis, may be possible. However, this regenerative process is sometimes inadequate because of an inefficient proliferative response by glomerular epithelial stem cells, as it may occur in aging patients or after FSGS (Figure 2).[40,70]

In addition, in some situations, an excessive proliferative response by glomerular epithelial stem cells will initiate new lesions, such as crescentic glomerulonephritis or collapsing glomerulopathy (Figure 3).[40,70] Thus, converging evidence indicates the type of pathologic or clinic presentation, or even the outcome of glomerular disorders, may depend on the balance between injury[1–16] and regeneration provided by glomerular epithelial stem cells.[29–33,38–40,70] Accord-

ingly, very recent results suggest that a Notch-regulated balance between podocyte loss and regeneration provided by renal progenitors influences the outcome of glomerular injury in adriamycin nephropathy.[81] Factors influencing the outcome of the regenerative process may also be the type, extension, or localization of podocyte injury, the age of patients, or patients genetic background. Understanding of how self-renewal and fate decisions of glomerular epithelial stem cells are perturbed or modulated will be of crucial importance in obtaining novel tools for the prevention and treatment of glomerulosclerosis.

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DISCLOSURES

None.

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