Podocyte Injury Can Be Catching

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Podocyte loss is a central mediator of glomerular sclerosis. Because podocytes are terminally differentiated cells that lack the potential to proliferate, they are particularly vulnerable to attrition in response to critical levels of cell stress, leading to detachment, necrosis, or apoptosis. Just how much podocyte loss is necessary to generate an initial sclerotic lesion and whether injury can propagate to other podocytes remain controversial.

Podocyte depletion and podocyturia have been documented in many chronic renal diseases, including FSGS, IgA nephropathy, and diabetic nephropathy, among others.1–3 The concept of podocyte depletion as a cause of glomerulosclerosis originates with the seminal ultrastructural studies by Nagata and Kriz4 in an ablation model of FSGS produced by uninephrectomy in the young rat. As glomeruli hypertrophy in response to loss of functioning nephrons, the terminally differentiated podocytes must stretch to provide cover for the enlarging glomerular tuft. The podocyte’s capacity to hypertrophy is limited, and sites of tuft denudation caused by individual podocyte failure and detachment become covered by parietal epithelial cells, forming a nidus for the development of segmental scars. This groundbreaking observation led Nagata and Kriz4 to formulate the thesis of podocytopenia in the development of segmental sclerosis.

More recently, investigators exploited genetic engineering in the mouse to test whether podocyte depletion per se is sufficient to cause FSGS. A number of ingenious toxin models can deliver a lethal dose of toxin specifically and exclusively to the podocyte, sparing all other renal cell types.5–7 By producing a transgenic animal that expresses a toxin receptor under the control of a podocyte-specific promoter, these models allow the severity of podocyte injury over time to be correlated directly with the onset, dosage, and duration of toxin exposure. In a transgenic rat model, human diphtheria toxin receptor was expressed under the podocin promoter.7 Because the rat homologue of the diphtheria toxin receptor does not recognize diphtheria toxin, only podocytes bearing the human receptor are able to internalize toxin. After injection of diphtheria toxin, which causes cell death by inhibition of protein synthesis, the extent of podocyte depletion correlates with the size of the segmental lesions and the severity of proteinuria. A threshold of 40% podocyte depletion produces the full-blown picture of FSGS with nephrotic proteinuria and reduction in renal function, whereas >60% loss leads to global sclerosis and severe renal failure.

In the NEP25 model, Matsusaka et al.6 produced a transgenic mouse that expresses human (h) CD25 driven by the neprhin promoter. FSGS develops within 2 to 4 weeks after injection of recombinant immunotoxin, a fusion protein composed of the variable domain of anti-hCD25 antibody and Pseudomonas exotoxin A as toxin moiety, which similarly kills cells by inhibition of ADP ribosylation of polypeptide chain elongation factor 2 that is required for protein synthesis. Whereas areas of denuded glomerular basement membrane (GBM) become covered by parietal epithelial cells,5,9 that migrate onto the tuft,5 only coverage by differentiated podocytes equipped with foot processes and slit diaphragms can reconstitute a normal glomerular filtration barrier.5

In this issue of JASN, Matsusaka et al.10 report a fascinating twist on the NEP25 toxin model devised to address the issue of local propagation of cell injury. By engineering a chimeric model in which only a subset of podocytes bear the hCD25 toxin receptor and the remainder are permanently genetically labeled with a durable tag, human placental alkaline phosphatase (PLAP), they have been able to map cell fate precisely after toxin exposure. Because the two mutually exclusive podocyte populations are variably admixed in individual glomeruli, this model has the advantage of producing a spectrum of chimeras in which from 2 to 99% of podocytes carry the toxin receptor, allowing a broad range of toxin effect to be monitored. In addition, because the PLAP tag is retained after injury, the receptor-negative podocytes can be identified even if they become dedifferentiated.

The provocative findings from this study shed new light into the ability of podocyte injury to propagate to neighboring cells that escape the initial insult.10 Toxin exposure produced rapid cell death in hCD25-positive podocytes with massive proteinuria at 4 days, followed by a wave of secondary injury to podocytes lacking the toxin receptor. In this later phase, which was evident 6 weeks after the initial assault, PLAP-positive podocytes display foot process effacement and downregulation of podocyte maturity markers, nephrin, podocin, and vascular endothelial growth factor together with upregulation of injury marker desmin. Importantly, the percentage of hCD25-negative podocytes with this dysregulated phenotype correlated with the percentage of hCD25-positive podocytes at baseline, indicating that the more cells that are damaged directly by toxin, the more toxin-resistant cells will be injured later in the secondary wave. The secondary injury often occurred at sites adjacent to sclerotic lesions, suggesting a phenomenon of localized cell-to-cell spread of injury that is driven by initial podocyte injury and loss, rather than a generalized adaptive response. By contrast, chimeras with few (<25%) toxin-sus...
ceptible cells actually seemed to stabilize or improve over time, supporting the existence of a critical threshold for irreversible glomerular scarring.

These observations find precedent in a conditional knock-out model of podocin, in which the severity of glomerulosclerosis far exceeds that predicted from the percentage of podocytes carrying the genetic defect. The findings are also congruent with long-term studies in the diphereria toxin model, in which proteinuria and urinary losses of nephrin-negative dedifferentiated podocytes persisted for months after a single brief injection of toxin, leading to glomerular destabilization and an autonomous cycle of progression to global glomerulosclerosis and renal failure.

What mechanisms underlie the local propagation of podocyte injury? Hypothetical mediators include loss of pro-survival factors such as nephrin signaling and vascular endothelial growth factor production or enhanced noxious factors such as TGF-β, angiotensin II, shear stress, or cell death gap junction signaling, none of which is mutually exclusive. Podocytes whose attachment to the GBM has been weakened by physical disruption of cell–cell contacts may be more vulnerable to detachment in response to filtration pressures. A functional consequence of podocyte loss, unremitting proteinuria itself, has also been shown to cause podocyte dedifferentiation and upregulation of TGF-β. Loss of favorable nephrin signaling after disruption of cell–cell contacts is an especially attractive mediator, not only because immunoreactivity for nephrin in this model was more readily lost than podocalyxin but also because nephrin is known to serve as a signaling platform for a host of vital cellular functions such as maintenance of polarity, cell–cycle regulation, and cytoskeletal organization. Podocytes interdigitate with other podocytes located within the same lobular unit of the glomerulus, which represents a major subdivision of the incoming afferent arteriole as it branches during glomerulogenesis. Loss of an interdigitating podocyte partner, by disrupting the physical integrity of the slit diaphragms themselves, could propagate injury to neighboring podocytes, like a domino effect, until the entire lobule is captured. This scenario would explain the exquisite segmentality of the sclerotic lesions, which seem to respect lobular boundaries early in the disease. Such biologic concepts are not unique to the kidney. In the brain, loss of neuronal–neuronal contacts after a localized injury to the gray matter can promote spreading depolarization and depression of electrical activity in adjacent healthy areas, causing lesion progression.

Several limitations of this study deserve mention. Although the authors demonstrate spread of injury to adjacent podocytes after toxin exposure, they do not quantify the extent to which these dysregulated toxin-resistant podocytes, in turn, are eventually lost by a mechanism of podocyte depletion. They also were unable to reproduce cell–cell injury in chimeric podocytes grown in culture. This is not surprising because the normal podocyte environment depends on the intricate association with GBM, mesangial, and endothelial cells under conditions of filtration that cannot be recreated faithfully in vitro. In fact, podocytes grown in culture lack true foot processes and slit diaphragms, hampering attempts to recapitulate the specialized cell–cell interactions found in the living organism. For these very reasons, the mechanisms of local propagation of injury are not likely to be operant in a simple culture system.

On the basis of these findings, the concept of progression of glomerular disease raises a new specter beyond traditional concepts of maladaptive responses mediated by up-regulation of the renin-angiotensin system, a process that fosters disease progression across nephrons over the long term. Local effects within the damaged glomerulus must now be viewed as potentially propagating injury to adjacent viable cells at the margins of a sclerotic lesion. These findings provide new insights into the unique, dynamic microenvironment that each individual podocyte inhabits and how it can turn hostile to survival. At the same time, they raise new therapeutic challenges to preserve glomerular function by containing podocyte injury and limiting its spread, both in podocytopenies and in other progressive glomerular diseases. This intriguing study lends fuel to the mounting paradigm shift in treatment of glomerular disease toward strategies aimed to enhance podocyte survival. Podocyte chimeras, although technically challenging, should provide an ideal modeling system to probe these effects.

DISCLOSURES
None.

REFERENCES

Declining Renal Function in Persons of Different Race without Chronic Kidney Disease

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“Plus ça change, plus c’est la même chose”—the more things change, the more they stay the same. Although this epigram is generally attributed to a 19th-century man of letters from France,1 it could easily have been coined by nephrologists in the United States with an interest in racial disparities in the burden of ESRD. Thus, two articles reporting outcomes seen in the initial years of ESRD coverage by Medicare note that hypertension and diabetes are the two most common causes, incidence rates are almost 3 times higher in African Americans, and survival was longer in African Americans than in Caucasians.

This ESRD paradox of higher incidence rates and longer survival remains unresolved to this day. Surprisingly, the recent explosion of research into quantifying the burden and risk factors of chronic kidney disease (CKD) has failed, so far, to cut the Gordian knot. Despite greater burdens of modifiable risk factors such as obesity, hypertension, and diabetes, creatinine-based GFR (GFRcreatinine) values are typically higher among minority populations. Of note, abnormal albuminuria is also overrepresented. This scenario of higher GFR and abnormal albuminuria finds an obvious parallel in classic type 1 diabetic nephropathy. Sadly, this parallel does not seem to apply: Racial disparities are not mitigated—if anything, they widen when levels of albuminuria are accounted for.

Most recent CKD models assume that loss of GFR proceeds in an orderly, linear fashion. In this model, GFR levels in two populations could reach a single (low) GFR level in different ways as follows: one subgroup starts at a higher GFR, and the disparity, if any, widened as GFR levels fell.

As the paradoxes have accumulated, so has concern that reliance on GFRcreatinine estimating equations may underlie these disparate findings.4 Hence, the findings of Peralta and colleagues in this issue of JASN are highly germane.5 Using the community-based Multi-Ethnic Study of Atherosclerosis da-

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See related article, “Podocyte Injury Damages Other Podocytes,” on pages 1275–1285.

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