Role of Podocytes in Focal Sclerosis: Defining the Point of No Return

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Podocyte dysfunction is linked to progressive glomerular filtration barrier failure and glomerulosclerosis. A detailed sequence of structural alterations is now used to define three general modes of podocyte damage, highlighting degenerative, inflammatory, or dysregulative pathways to glomerulosclerosis (1).

In this issue of JASN, three reports offer novel insights into the causal relationship between podocyte damage and glomerulosclerosis and define specific markers that identify the “point of no return” in glomerular filtration barrier failure. The authors have focused on the following questions:

Is There a Causal Relationship between Lack of Podocytes and Progressive Glomerulosclerosis?

Over the last 15 yr, much evidence has been accumulated correlating podocyte loss with progressive glomerulosclerosis (2). To date, direct evidence that podocyte depletion is sufficient to cause glomerulosclerosis was lacking. Transgene technology was used to experimentally address this question. Matsusaka et al. selectively depleted podocytes in adult mice transgenic for the human CD25 with an anti-CD25 immuno-toxin, resulting in a dose dependent induction of glomerulosclerosis (3). Using the diphtheria toxin in rats with podocytes transgenic for the human diphtheria toxin receptor, Wharram et al. were able to titrate the administration of toxin to induce defined levels of podocyte depletion (4). The rats used in this study showed dose-dependent structural alterations with all of the characteristic features of focal segmental glomerulosclerosis. Both reports provide experimental evidence for the essential role of podocytes in glomerular function.

Does the Degree of Podocyte Loss Correlate with Defined Stages of Glomerular Damage?

Wharram et al. show that a depletion of <20% of podocytes caused transient proteinuria and mesangial expansion, loss of 20 to 40% podocytes resulted in persistent proteinuria and focal glomerulosclerosis, but no progressive decline in renal function, and >40% podocyte loss caused progressive glomerular failure.

In the second study reported by the Wiggins group, a different approach led to comparable conclusions (5). Fischer 344 rats show spontaneous, aging-associated glomerulosclerosis. Surprisingly, quantification of glomerular cells and volumes in these rats was not able to show an age-related loss of podocytes, but a considerable glomerular hypertrophy with aging.

Why Would Glomerular Hypertrophy Cause a Similar Phenotype as Seen with Podocyte Depletion?

The key aspect of podocyte function is the maintenance of a defined surface of the glomerular filtration area. A loss of podocytes or an increase in filtration area to be served (with stable podocyte number) should result in increased demands on the remaining podocytes. In the study of aging rats, glomerular volume appears to be outgrown podocyte hypertrophic capacity at the 24th month of life. This lead to a 60% decrease in podocyte per glomerular volume (also referred to as podocyte density) (5), comparable to the reduction in podocyte density causing progressive glomerular damage shown in the depletion study (4). As calorie restriction can prevent age-related alteration in Fischer 344 rats, aging lean rats were evaluated for their glomerular phenotype. These animals showed an intact filtration barrier. In keeping with the concept of a critical threshold of podocyte depletion, these rats had decreased their podocyte density only by 30%. As predicted from the depletion study (4), the lean rats did not show parameters of podocyte stress or glomerulosclerosis (5).

Are There Specific Diagnostic Parameters That Can Be Used to Define the Critical Stages of Podocyte Stress in Glomerular Disease?

Defining a threshold of podocyte depletion/stress-causing progressive glomerular disease would have far-reaching clinical consequences. How do these findings in rat models compare with available human studies? Correlating podocyte numbers with the degree of glomerular damage, comparable thresholds of podocyte density had been obtained in human diabetic nephropathy, with microalbuminuria seen with 20% and clinical nephropathy with 40% podocyte loss (6). Similar results were obtained for podocyte damage in IgA nephritis (7).

Should we start to determine podocyte density in human renal biopsies to assess the level of podocyte stress? Aside from the technical issues that would have to be overcome, a major limitation of this approach would be the considerable number of glomeruli required for robust morphometric studies. An
alternative strategy is the noninvasive monitoring of loss of podocytes in the urine, an approach that is currently being evaluated for its predictive power (8–10). Urinary podocyte levels could serve as a general marker of ongoing glomerular damage, but could not in itself be used as an estimate of the functional reserve maintained in the individual patient.

Wiggins et al. used genome-wide expression profiles in the aging rats to screen for markers of defined levels of podocyte stress (5). A repression of molecules intimately linked to podocyte function (nephrin, WT1, GLEPP1) was seen at onset of progressive proteinuria in the decompensation stage. Can comparable markers be identified in human glomerular aging and disease? Initial data from a cohort of pretransplant biopsies taken from living donors shows a similar result with a significant negative correlation between donor age and glomerular expression of podocyte-specific markers (Lemley and Kretzler, unpublished observation). In preliminary studies of human glomerular disease and aging, the desmin to nephrin ratio was not found to correlate as clearly with podocyte stress as in the aging rats (author’s unpublished observation). The hope is that large-scale mRNA expression screening approaches currently underway in human glomerular disease will yield similar clear-cut markers for human podocyte stress (11). To identify molecular parameters of glomerulosclerosis, an additional approach has been added to our toolbox. Using the 5/6 nephrectomy rat model, Xu et al. (12) were able to generate reproducible proteomic signatures from laser-microdissected glomerular crosssections. The signatures obtained not only separated sclerotic from normal glomeruli, but also gave a specific pattern for presclerotic glomeruli. In a second step, thymosin β4 was identified to contribute to the differential proteomic signature and can now be evaluated as an early marker of glomerulosclerosis.

Can We Prevent or Even Treat Decreased Podocyte Density and Stress?

If glomerular sclerosis is indeed, as stated by Wiggins, a cell-depletion disease, could it be a target for the emerging field of regenerative medicine? Considering the unique anatomical and functional environment of the podocyte, it appears to be exquisitely difficult to reload an actively filtering glomerulus with podocytes integrated into the complex three-dimensional network of interdigitating foot processes. Introducing proliferative podocyte precursor cells into a damaged glomerulus might have disastrous consequences, as it could lead to scenarios resembling podocyte proliferation in collapsing glomerulopathy (1).

As podocyte density is defined not only by podocyte number, but also by glomerular surface area, targeting glomerular hypertrophy is the alternative approach and has proven to be an effective therapeutic strategy for progressive glomerular disease. In this context, the prevention of glomerulosclerosis by dietary restriction in the aging Fischer rats reported by Wiggins is remarkable (5). Observational studies have shown a close correlation of obesity with progression of renal disease (13), most strikingly in humans with reduced renal mass (14). As addressed also by several recent manuscripts and editorials in JASN (15,16), aggressive management of this risk factor is warranted with an aging, obese population at the doorsteps of our clinics.

The study of podocytes in glomerular filtration barrier failure has come of age. The experimental insight gained by combining transgene technology with genomic and proteomic tools is starting to provide the molecular basis for disease stage classification, diagnostic parameters for rapid assessment of therapies, and paths to open new therapeutic avenues.

References


