Morphology expands understanding of lesions

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Nephrin's role in the podocyte

Holzman LB, St. John PL, Kovari IA, et al. Nephrin localizes to the slit pore of the glomerular epithelial cell: rapid communication. Kidney Int. 1999;56:1481–1491. For many years since renal biopsies entered the armamentarium of the nephrologist, the standard approach to assessment was light microscopy with gradual addition of selected special stains, immunofluorescence, and then electron microscopy. An explosion in understanding of the spectrum of etiologies underlying the limited repertoire of lesions in the kidney, coupled with in-depth mining of morphologic lesions and their implications for prognosis, has ensued over the last decades. An exciting direction for exploration of new information for pathogenesis of glomerular diseases was driven by the seminal observation that mutations in nephrin were causal in congenital nephrotic syndrome of Finnish type.[1] This observation was followed by the beautiful studies by Holzman *et al.*[2] These studies provided a detailed initial characterization in the mouse of the nephrin protein, coded by the *Nphs1* gene. Holzman *et al.*[2] cloned and sequenced the full-length cDNA of the nephrin open-reading frame and developed an immunoaffinity-purified polyclonal antiserum against the cytoplasmic domain. They identified nephrin as a glycoprotein that was located in the kidney only in visceral glomerular epithelial cells at the junction between mature podocyte foot processes. Nephrin immunostaining positivity was detected even in the newborn mice during early stages of development when the earliest slit pores and slit diaphragms were developing. From these carefully done studies of morphology made possible by the development of novel tools, Holzman *et al.*[2] could show the localization of nephrin. They also suggested that nephrin was a putative cell adhesion molecule of the immunoglobulin superfamily. These early studies were foundational for subsequent additional work confirming that nephrin is a key component of the slit diaphragm.

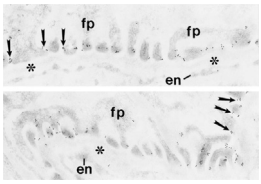

Figure 1|

Figure 1 is reprinted with permission from Holzman LB, St. John PL, Kovari IA, et al. Nephrin localizes to the slit pore of the glomerular epithelial cell: rapid communication. *Kidney Int.* 1999;56:1481–1491.[2] Copyright © 1999 International Society of Nephrology.

Plasticity of podocytes

Bariéty J, Nochy D, Mandet C, et al. Podocytes undergo phenotypic changes and express macrophagic-associated markers in idiopathic collapsing glomerulopathy. Kidney Int. 1998;53:918–925. Additional studies of podocytes showed the plasticity of these terminally differentiated cells.[3] Bariéty *et al.*[3] studied a small group of patient biopsies that had idiopathic collapsing glomerulopathy, characterized by collapse of the glomerular tuft and overlying proliferation of the visceral epithelial cells. They showed that in addition to the morphologic changes of swelling of these cells with vacuolization, multinucleation, and proliferation, these cells did not express the typical markers of podocytes such as podocalyxin, vimentin, and complement receptor 1. Rather, these cells showed macrophage-associated epitopes. These early studies indicated that not all cells in a visceral epithelial cell location show a podocyte

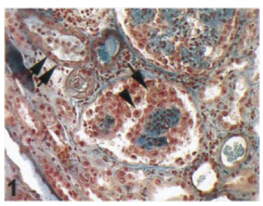

Figure 2|

Editor's Note

This article is part of the *Kidney International* 60th anniversary series. This month's topic is insights from study of renal morphology.

phenotype. Subsequent work has shown that parietal epithelial cells may populate the tuft, and that these proliferating visceral epithelial cells indeed show parietal epithelial cell markers.[4–6] Further studies subsequently illustrated the plasticity of the visceral epithelial cells using lineage-tracing mice. After injury, parietal epithelial cells could reach the glomerular tuft and either contribute to sclerosis or potentially in certain settings, including development and some diseases, potentially become podocyte-like.[6–8]

Figure 2 is reprinted with permission from Bariéty J, Nochy D, Mandet C, et al. Podocytes undergo phenotypic changes and express macrophagic-associated markers in idiopathic collapsing glomerulopathy. *Kidney Int.* 1998;53:918–925.[3] Copyright © 1998 International Society of Nephrology.

Podocyte loss linked to glomerulosclerosis

Kim YH, Goyal M, Kurnit D, et al. Podocyte depletion and glomerulosclerosis have a direct relationship in the PAN-treated rat. Kidney Int. 2001;60:957–968. Further studies of the key role of podocytes were pursued by Kim *et al.*[9] In elegant studies in the puromycin aminonucleoside (PAN) rat model of podocyte injury, they observed decrease in podocyte glomerular count, with detached podocytes within Bowman's space and terminal deoxynucleotidyl transferase–mediated dUTP nick end-labeling–positive apoptotic podocytes within the glomeruli. With additional injections of PAN, further podocyte depletion resulted in glomerulosclerosis, the extent of which correlated with the loss of podocytes. This was among the early studies showing that an insufficiency of podocytes (i.e., decreased podocyte number relative to tuft area) could lead to further loss of podocytes and eventual sclerosis. Taken together, the above-mentioned studies showed the importance of key structural podocyte molecules in maintaining health, and that injury of podocytes or mutation of key podocyte structural proteins can cause glomerulosclerosis. The key role of podocyte depletion to development of glomerulosclerosis has led to many efforts to understand factors leading to podocyte loss and injury, both genetic and acquired injuries.

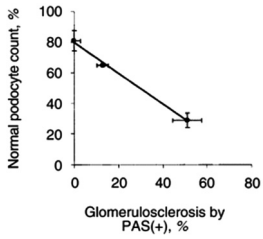

Figure 3 |

Figure 3 is reprinted with permission from Kim YH, Goyal M, Kurnit D, et al. Podocyte depletion and glomerulosclerosis have a direct relationship in the PAN-treated rat. *Kidney Int.* 2001;60:957–968.[9] Copyright © 2001 International Society of Nephrology.

Novel entity linked to monoclonal protein deposition

Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004;65:85–96. In addition to the above-mentioned findings focused on understanding of the epithelial cells of the glomerulus, in-depth studies of human diseases from clinical renal biopsies have led to new insights. The recognition that diffuse endocapillary proliferative or membranoproliferative glomerulonephritis lesions could be mediated by monoclonal protein was initially made by detailed studies from Nasr *et al.*[10] In their initial report, 10 patients were observed with biopsies that showed proliferative glomerulonephritis, staining with IgG and with usual appearance of the deposits by electron microscopy, such as that seen with immune complex-mediated glomerulonephritis. However, the immunofluorescence studies also importantly included staining for kappa and lambda. These cases were clonal, expressing only 1 light chain, with 6 with kappa and 4 with lambda in this initial series. Additional studies with staining for IgG subclasses confirmed corresponding heavy chain clonality, with 3 cases showing IgG1, 1 showing IgG2, and the remainder showing IgG3 restrictions. All of the deposits contained the 3 constant domains of the gamma heavy chain, CH1, CH2, and CH3. Complement was present within the tissue, and about one-half of the patients had hypocomplementemia. Patients presented with moderate renal insufficiency and nephrotic-range proteinuria. In this initial series, a monoclonal protein was present in the serum in one-half the cases. Subsequent larger series have shown that IgG3 kappa is the most common clonality in this entity, and only 30% of patients in larger series have a detectable circulating monoclonal protein matching that

Figure 4 |

which is deposited in the kidney. Only rarely over long follow-up do patients develop overt multiple myeloma.[11] The disease often recurs in the allograft. This observation, based on careful study of clinical biopsies, has expanded the understanding of the types of diseases that may be caused by monoclonal proteins. There also is a challenge when treating these patients without a serum marker to use as a benchmark for response to any therapy directed at the underlying monoclonal process. Adding to the complexity of interaction of monoclonal proteins and kidney disease, additional studies have pointed to the possibility that a monoclonal protein, rather than depositing in the kidney causing the above lesion or other monoclonal deposition disease, may trigger complement dysregulation and result in a C3 glomerulonephritis.[12] In these patients, no monoclonal protein is deposited in the kidney, but complement is dysregulated and massive C3-dominant deposits are detected by immunofluorescence and electron microscopy. In some, treatment of the underlying monoclonal protein has had beneficial effect on the C3 glomerulopathy.

Figure 4 is reprinted with permission from Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. *Kidney Int.* 2004;65:85–96.[10] Copyright © 2004 International Society of Nephrology.

IgA nephropathy morphologic risk factors defined

Roberts ISD, Cook HT, Troyanov S, et al., for the Working Group of the International IgA Nephropathy Network and Renal Pathology Society. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76:546–556.

Cattran DC, Coppo R, Cook HT, et al., for the Working Group of the International IgA Nephropathy Network and Renal Pathology Society. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–545. This discussion demonstrates that reporting of details of kidney morphology may lead to recognition of new disease entities and novel causalities. In addition, careful unbiased dissection of lesions in well-known entities may lead to new insights of prognostic implications of various lesions. Such an unbiased, evidenced-based approach was used in key studies led by the International IgA Nephropathy Network, in collaboration with the Renal Pathology Society, culminating in the Oxford classification of IgA nephropathy.[13,14] The classification is named for Oxford, United Kingdom, where many meetings of nephrologists and pathologists took place over several years. Archival biopsies with well-characterized IgA nephropathy patients were studied. All lesions were carefully defined, and iterative working groups then determined those pathologic variables that could be reproducibly scored. In this initial cohort of some 250 patients, excluding those that reached end-stage kidney disease within a year, 6 parameters could be reproducibly scored. These lesions were then analyzed *vis-à-vis* the clinical follow-up of these patients independent of the clinical data. The variables assessed included the degree of mesangial hypercellularity, the extent of glomerular segmental sclerosis, endocapillary hypercellularity, the presence of cellular or fibrocellular crescents, the degree of interstitial fibrosis/tubular atrophy, and arteriosclerosis. Of these, 4 variables independently correlated with worse outcome. Of note, this study did not adequately include cases with crescent. A larger follow-up study has since shown that crescents, with fibrocellular or cellular, also were associated with worse outcome.[15] If these crescents involved <25% of glomeruli, prognosis was not worse if patients received immunosuppression. With greater extent of crescents, prognosis was worse even with immunosuppressive treatment.

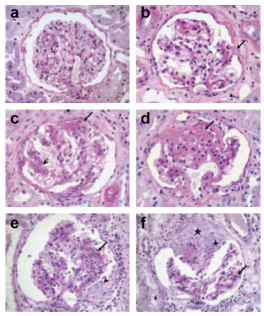

Figure 5 |

Figure 5 is reprinted with permission from Roberts ISD, Cook HT, Troyanov S, et al., for the Working Group of the International IgA Nephropathy Network and Renal Pathology Society. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int.* 2009;76:546–556.[13] Copyright © 2009 International Society of Nephrology.

These selected papers highlight only some of the remarkable advances published in *Kidney International* that enhance our understanding or the etiology and molecular basis for some of the lesions that develop in various kidney diseases.

DISCLOSURE

The author declared no competing interests.

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