Glomerular Disease: Looking beyond Pathology


Abstract
The National Institute of Diabetes and Digestive and Kidney Diseases–supported Kidney Research National Dialogue asked the scientific community to formulate and prioritize research objectives aimed at improved understanding of kidney function and disease progression. Over the past 2 years, 1600 participants posted almost 300 ideas covering all areas of kidney disease. An overriding theme that evolved through these discussions is the need to move beyond pathology to take advantage of basic science and clinical research opportunities to improve diagnostic classification and therapeutic options for people with primary glomerular disease. High-priority research areas included focus on therapeutic targets in glomerular endothelium and podocytes, regenerating podocytes through developmental pathways, use of longitudinal phenotypically defined disease cohorts to improve classification schemes, identifying biomarkers, disease-specific therapeutics, autoantibody triggers, and changing the clinical research culture to promote participation in clinical trials. Together, these objectives provide a path forward for improving clinical outcomes of glomerular disease.


Introduction
Primary glomerular disease affects both children and adults, causes about 10% of ESRD, and costs approximately 1% of Medicare dollars for RRTs. This commentary focuses on a subset of the currently pathologically defined primary inflammatory and noninflammatory glomerular diseases, including membranous nephropathy (MN), minimal change disease (MCD), FSGS, and IgA nephropathy (IgAN). Despite their importance, knowledge of their pathogenic origins and effective therapies remain limited.

The National Institute of Diabetes, Digestive, and Kidney Diseases sponsored the Kidney Research National Dialogue to identify critically important research objectives and facilitate community-wide strategic planning. An overriding theme that evolved through these discussions is the need to move beyond pathology by integrating basic research and clinical approaches to develop new classifications and novel therapeutic targets as a way to improve patient outcomes (Figure 1).

The glomerulus is a specialized structure adapted for filtration and regulating body homeostasis. Its specialized cells (endothelial, mesangial, juxtaglomerular, and parietal epithelial cells and podocytes) are resident on and contribute to specialized matrix structures (glomerular basement membrane [GBM] with its constituent proteins, mesangium, and Bowman’s capsule). During disease, these cells and structures become the target of disordered innate and adaptive immune, complement, and other host defense and regulatory mechanisms that derange carefully orchestrated feedback loops between these cells and structures. Patients develop a specific disease from a unique combination and integration of genetic susceptibilities, environmental factors, and epigenetic changes. Disease classification is currently based on pathologic changes observed on renal biopsy; however, improved understanding of pathophysiologic mechanisms will likely change this classification schema. Although inhibition of the renin-angiotensin-aldosterone system and nonselective immunosuppression and/or suppression of inflammation are mainstays for mitigating glomerular diseases, relatively little is known about other pathways and their potential for therapeutic intervention. Below are areas of focus that require additional research.

Glomerular Endothelium
The initial point of contact between the immune cells in circulation and the renal tissue is the large surface area of the vascular glomerular endothelium, particularly the glyocalyx that coats the glomerular endothelial cells. The vascular endothelium is a major site of inflammation, T-cell autoreactivity, leukocyte recruitment and diapedesis, and the target of both cellular- and humoral-mediated immune responses. Therefore, delivering therapeutic interventions to the renal endothelium, particularly in glomeruli, represents a potential target for intervention.

Podocyte Plasticity and Development
Podocyte plasticity is a feature of proteinuric glomerular diseases that may represent a reversal of the podocyte developmental process. A better understanding of underlying mechanisms involved in podocyte development (signaling cascades, genetic and transcriptional regulation, intracellular protein trafficking, and autophagic degradation) is needed. Other areas of
interest include the identification of podocyte progenitor cells in developing kidneys, residual niches of progenitors in the mature kidney, and whether podocytes are terminally differentiated cells. Factors regulating developmental transitions in the adjacent GBM (including laminin and collagen IV isoforms) must be identified, because they might overlap with those factors that regulate synthesis of slit diaphragm components. It may also be instructive to look at podocyte maturation and GBM matrix deposition, because they occur in disease models, and compare them with normal kidney embryogenesis and development.

**Autoantibody Triggers**

Anti-GBM, anti-ANCA, antiphospholipase A$_2$ receptor antibody (anti-PLA$_2$R), and IgG antibodies against aberrantly glycosylated IgA1 antibody are now established as pathogenic autoantibodies in Goodpasture disease, ANCA-associated vasculitis, MN, and IgAN, respectively. However, the primary events that trigger loss of tolerance to these autoantigens remain a mystery. Each of these diseases provides a potentially tractable approach to effective therapy aimed at upstream causation. Achieving the ultimate goal of restoring self-tolerance in these autoimmune diseases will require fine mapping of the primary epitope and identifying specific antigen recognition partners in the immune system. Realization of this opportunity will require cooperation between immune chemists, basic immunologists, and nephroscien-tists. Although animal models are important tools to refine and test what is learned in human biology, human translational studies are a sine qua non.
For example, circulating anti-PLA2R antibody in MN provides a diagnostic tool that should efficiently guide therapies and serve as a surrogate for clinical trials. The goal of restoring self-tolerance notwithstanding, it should be possible to develop affinity absorption strategies to remove pathogenic Ig and design small blocking molecules to inhibit binding to antigens. There is also a window of time from active antibody deposition until effective immune activation when targeted inhibition of complement may prevent ongoing injury.

Mechanisms by which nephrotic syndrome associated with diffusely effaced foot processes can be either steroid-sensitive or -resistant, and often (but not always), they are accompanied by FSGS; these mechanisms remain poorly understood. Genetic studies for the majority of single gene mutations associated with MCD and/or FSGS phenotypes, accompanied by careful clinical phenotyping, will help define major pathways. The role of podocyte-secreted angiopoietin-like 4 in driving pathologic MCD nephrotic syndrome and soluble urokinase-type plasminogen activator receptor- and cluster of differentiation 80-targeted therapies for FSGS-like phenotypes are potentially important advances that remain to be confirmed. The mechanisms by which Apolipoprotein L1/myosin heavy chain 9 confers risk in the African-American population need to be better understood to develop effective therapeutic approaches to prevent disease progression.

IgAN is the most common primary glomerular disease, but the clinical relevance of genetic loci associated with disease remains poorly defined. Although the elucidation of immunologic targets of unique chemical bonds and abnormally glycosylated IgA has advanced rapidly, the clinical science has not. There is a need for surrogate markers of response that correlate with definitive outcomes (i.e., organ and patient survival), and it remains undetermined whether histologic improvement after treatment is an adequate response measure.

**Patient Cohorts for Longitudinal History, Classification, and Individualized Medicine**

Glomerular disease classifications are currently based on histologic criteria, and patients are typically treated with a few nonspecific immune-modulating agents. However, individual complexity may be better explained by deriving new subgroups based on a wider range of information, including genetic, epigenetic, and environmental exposures; upstream immune or nonimmune mechanisms; downstream pathophysiologic pathways; and responsiveness to different classes of drugs. This information can then be integrated to develop and validate individualized pathways and biomarkers that inform the design of optimized, patient-specific interventions. Unraveling this complexity cannot be done in animals but requires cohorts of accurately phenotyped patients that are followed long-term through disease exacerbations and remissions. Complex analytic tools are needed to integrate phenotype information with omic information from blood, urine, and tissue. Identified pathways, regulatory hubs, targets, and potential interventions can be tested in high-throughput model systems (e.g., zebrafish or fruit fly). It will then be critical to learn how to define individualized risk and effectively implement preventive strategies in a cost-effective manner.

**Promoting Glomerular Disease Research**

A change in culture is needed to emulate the pediatric oncology and cystic fibrosis fields that actively encourage scientific collaboration and participation in clinical studies and trials. This cultural change can be driven by nephrologists, disease-based advocacy groups and foundations, and patients through self-identification and registries.

**Summary**

Capitalizing on the opportunities afforded by new scientific advances in general and glomerular science in particular will require collaboration of clinicians, scientists, and patients working together. Each primary glomerular disease is driven by particular upstream immune or nonimmune mechanisms that require focused molecular definition, specific biomarker development and validation, and targeted intervention strategies. Circulating anti-PLA2R antibody in MN serves as a paradigm for this approach. Individualized medicine approaches may be useful to provide individualized pathway analysis for drug targeting. A focus on the glomerular endothelium and podocytes is likely to yield payoff in terms of biomarker development and novel therapies. Translation to the clinic requires continued development of phenotypically defined patient cohorts for biosample acquisition, biomarker validation and drug testing, patient cooperation, and advocacy. We hope that the identification of these broad themes will help to move glomerular disease beyond pathology to focus on basic science and clinical research opportunities to improve patient outcomes.

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**Disclosures**

L.B.H. is a consultant for GSK and Bristol Meyer Squibb. S.S.C. is Founder, President, and Chief Executive Officer of GDTherapy LLC and has filed patents related to the use of Angpt4 mutants (PCT/US2011/039255) and precursors of sialic acid, including ManNac (PCT/US2011/039058), for the treatment of nephrotic syndrome. He may benefit financially from these patents in the future. H.T. is a consultant for Retrophin, Inc., Kaneka, Corp., and Otsuka, Inc. He is on the American Board of Pediatrics Nephrology Subboard Self-Assessment Program and is the editor for the Nephrology Self-Assessment Program issue on pediatric nephrology. The remaining authors report no disclosures.

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