Novel Biomarkers in Glomerular Disease

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Glomerular diseases are major contributors to the global burden of end-stage kidney disease. The clinical course and outcome of these disorders are extremely variable and difficult to predict. The clinical trajectories range from a benign and spontaneously remitting condition to a symptomatic and rapidly progressive disease. The diagnosis is based entirely on the evaluation of kidney biopsy, but this invasive procedure carries multiple risks and often fails to predict the clinical course or responsiveness to treatment. However, more recent advances in genetics and molecular biology have facilitated elucidation of novel pathogenic mechanisms of these disorders. These discoveries fuel the development of novel biomarkers and offer prospects of noninvasive diagnosis and improved prognostication. Our review focuses on the most promising novel biomarkers that have recently emerged for the major types of glomerular diseases, including immunoglobulin A nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis.

Key Words: Glomerular disease, Immunoglobulin A nephropathy, Membranous nephropathy, Focal segmental glomerulosclerosis, Membranoproliferative glomerulonephritis

Glomerular diseases are an important group of kidney disorders and collectively represent a major cause of ESRD worldwide. The presentation, clinical course, and outcome of glomerular diseases are highly variable. Some patients achieve complete spontaneous remission whereas others progress rapidly to ESRD despite aggressive treatment. Although kidney biopsy is the gold standard for the diagnosis and evaluation for treatment, it is invasive and has several serious complications. In many cases, histopathology is neither diagnostic nor prognostic and it fails to predict response to therapy, likely because many heterogeneous pathogenetic mechanisms generate clinically indistinguishable histology. Thus, beyond histopathological evaluation, clinical biomarkers of specific pathogenic processes may improve subclassification and facilitate therapeutic choices. This review provides an update on the most promising glomerular disease biomarkers tested in clinical studies of 4 major types of glomerular diseases: immunoglobulin A (IgA) nephropathy (IgAN), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and membranoproliferative glomerulonephritis (MPGN).

IgAN

IgAN is the most common form of primary glomerulonephritis. The clinical spectrum of IgAN covers a wide range of features, from minor urinary abnormalities to rapidly progressive kidney failure. In general, approximately 20% to 40% of patients with IgAN develop ESRD within 20 years of diagnosis.[1-3] The disease is characterized by mesangial deposition of polymeric IgA1. The diagnosis is based entirely on the examination of kidney biopsy tissue and is defined by dominant or codominant glomerular immunoglobulin A (IgA) staining. Many studies established that abnormal O-glycosylation of IgA1 represents 1 of the key pathogenic events in IgAN. The defective glycosylation pattern involves galactose deficiency in the side chains of O-linked glycans attached to the hinge region of IgA1 heavy chains. The galactose-deficient IgA1 (Gd-IgA1) is present in the mesangial immune deposit, and its serum level is quantifiable by enzyme-linked immunoabsorbent assay (ELISA). However, a high level of circulating Gd-IgA1 alone does not induce kidney injury, and additional factors are likely required for the full expression of nephritis. Current data indicate that at least 4 hits may contribute to development of IgAN: aberrant glycosylation of IgA1 (hit #1), synthesis of antibodies directed against Gd-IgA1 (hit #2), formation of circulating immune complexes (hit #3), and deposition of these complexes in the glomerular mesangium (hit #4).[4-6] The deposits promote glomerular inflammation, cause local activation of the complement system, and stimulate proliferation of mesangial cells. For a more extensive overview, we refer the interested reader recent extensive reviews on the genetic,[5] immunologic,[7] and clinical [6] aspects of this disease.

Clinical Markers

Predictors of kidney failure in IgAN have been assessed in several clinicopathologic studies; baseline clinical factors most consistently found to be independently associated with progressive kidney disease include decreased kidney function at the time of diagnosis,[8-11] histologic grading,[8-12] and proteinuria.[12-14] Some studies suggest

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an additional predictive value of age,[11] gender,[11] high blood pressure at presentation,[5-7] serum albumin level,[11,15] hematuria,[11] and family history.[9,11] More recently, a helpful clinical progression risk score has been proposed that estimates the probability of ESRD based on 4 clinical variables at the time of renal biopsy: estimated glomerular filtration rate, systolic blood pressure, hemoglobin, and serum albumin level (see Web Resources for online calculator).[16] Although this simple risk score outperformed previously proposed kidney disease progression scores, it was designed based on a single Chinese cohort and will require prospective validation in Caucasians.

Histopathologic Markers

On biopsy, IgAN is characterized by focal mesangial proliferation and matrix expansion accompanied by mesangial deposits of IgA and often weaker staining for immunoglobulin G (IgG), C3, and C5b-9. Although several histopathological classifications for IgAN have been proposed, older scoring systems had generally poor correlation with clinical outcomes. Recently, a new Oxford classification system has been proposed based on 4 histologic criteria that best correlate with disease progression: mesangial proliferation (M), endocapillary proliferation (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T).[17] In the validation studies, the T-score is most consistently associated with poor prognosis whereas the E-score appears least reproducible.[18,19] Although the Oxford scoring system does not include crescentic lesions, follow-up studies and clinical experience suggest that crescents represent an important prognostic factor,[18] and the crescent (C) score may be included in future modifications of this classification. In addition to the type of histologic lesions, tissue markers of complement activation, such as intensity and pattern of staining for C3, C4d, C5b-9, and mannose-binding lectin, may offer supplemental information about disease activity.[20-22]

CLINICAL SUMMARY

- The most promising biomarkers for IgAN include serum Gd-IgA1, serum anti-glycan antibody levels, and the genetic risk score developed based on GWAS susceptibility loci.
- The most promising biomarkers for MN include anti-PLA2R antibodies and genetic variants in HLA and PLA2R identified in GWAS.
- The most promising biomarkers for FSGS include serum suPAR, podocyte CD80 staining, and genetic variants in APOL1 in individuals of African ancestry.
- C3 glomerulopathies are due to the alternative complement pathway overactivity, caused either by rare genetic defects or acquired antibodies against complement components.

Blood Markers

The serum levels of Gd-IgA1 and anti-glycan antibodies directed against the hinge region of Gd-IgA1 represent the most promising candidate biomarkers for IgAN.[23,24] A lectin-based ELISA assay for circulating Gd-IgA1 demonstrates 90% specificity and 76% sensitivity to diagnose IgAN; thus, it appears to be 1 of the best candidates for a new, noninvasive diagnostic test.[23] However, this test uses a naturally occurring lectin and has been difficult to standardize; thus, it has not yet been introduced in routine clinical practice. Using this assay, a recent study from China suggested that high level of Gd-IgA1 at the time of diagnosis was associated with a faster rate of kidney function decline.[25] These observations are promising, but they will require replication in independent cohorts. It is interesting to note that the glycosylation defects appear to have a strong genetic determination with heritability of over 50%.[26,27] In family-based studies, it became apparent that many of the asymptomatic relatives of IgAN cases have elevated Gd-IgA1 in the absence of kidney disease, suggesting that elevated Gd-IgA1 level alone is not sufficient to produce clinically significant disease. These observations suggest that additional factors (or "hits") are required for full disease expression. The formation of anti-glycan antibodies directed at the hinge region of Gd-IgA1 emerged as 1 of the most likely candidates for a "second hit."[24] The test for anti-glycan antibodies could be used in combination with Gd-IgA1 levels to identify patients at high risk of disease. Moreover, early studies indicate that elevated levels of anti-glycan IgGs in the sera of patients with IgAN correlate well with proteinuria[24] and may predict faster progression to ESRD.[28] More formal evaluation of the diagnostic and prognostic utility of Gd-IgA1 levels in combination with anti-glycan antibody titers awaits well-designed clinical studies.

Urine Markers

There are currently no reliable urinary markers with clinical utility in IgAN. Several candidates have been studied with variable success, including urinary levels of immune complexes containing Gd-IgA1[29] and urinary markers of complement activation, such as C5b-9, factor H (FH), mannose-binding lectin, and properdin levels.[30,31] Newer approaches that are based on the analysis of the urinary proteome offer prospects to identify novel candidate peptides,[32-34] but applications to IgAN have been limited. Likewise, urinary RNA profiling, including microRNAs (short noncoding RNA molecules that regulate gene expression), may offer completely novel molecular markers,[35-37] but initial studies in IgAN suffer from small sample sizes.