Progress in IgA Nephropathy and Its Clinical Implications

By Pietro A. Canetta

In the past several years, major progress has been made in understanding the mechanisms underlying the development and progression of IgA nephropathy (IgAN). These advances have contributed to the generation of an ever-expanding catalog of measurable variables that provide diagnostic or prognostic information about IgAN. Such measures span the gamut from immune mediators and metabolites detectable in serum or urine, to genetic and epigenetic traits, to histologic features both traditional and novel. IgAN has a complex multistep pathogenesis involving essentially every branch of the immune system, and this progress in measurable variables holds great promise for better characterizing the disease and, in turn, allowing for a more nuanced approach to prognosis and therapy.

The modern understanding of IgAN pathogenesis centers on the creation and deposition of IgA-containing immune complexes in the glomerular mesangium (Figure 1) (1).The earliest step appears to be the development of elevated circulating levels of poorly glycosylated immunoglobulin A1, known as galactose-deficient IgA (Gd-IgA1). This alone is insufficient to cause disease because elevated Gd-IgA1 levels are also found in healthy relatives of IgAN patients. Next, either IgA or IgG antibodies are formed that bind to Gd-IgA1, leading to the development of immune complexes. There are many hypothesized triggers for this autoantibody production, but a common theme is activation of mucosal immunity, especially in the tonsillar or intestinal lymphoid tissue. As immune complexes form or are deposited in the renal mesangium they activate local inflammatory cascades whose final common pathway is cell proliferation, matrix production, and eventually glomerular sclerosis and interstitial fibrosis. In this final stage of pathogenesis, IgAN becomes clinically apparent, with hematuria, proteinuria, and eventual loss of glomerular filtration.

Two key measurable elements of the pathogenic mechanism are circulating Gd-IgA1 and the antiglycan autoantibodies. Studies have separately demonstrated that both elevated Gd-IgA1 levels and elevated antiglycan levels predict an increased risk for kidney failure, and at least one study of longitudinal measurements has directly correlated the level of these biomarkers with disease activity (2). Validation of these findings and the development of reliable, affordable, and commercially available assays could provide a much needed biomarker of immune activity, perhaps akin (and hopefully superior) to DNA antibodies in systemic lupus erythematosus or ANCA levels in pauci-immune glomerulonephritis. This would represent a major advance in the clinical approach to IgAN, supplementing the current time-tested but entirely nonspecific standards of disease activity, proteinuria, and serum creatinine.

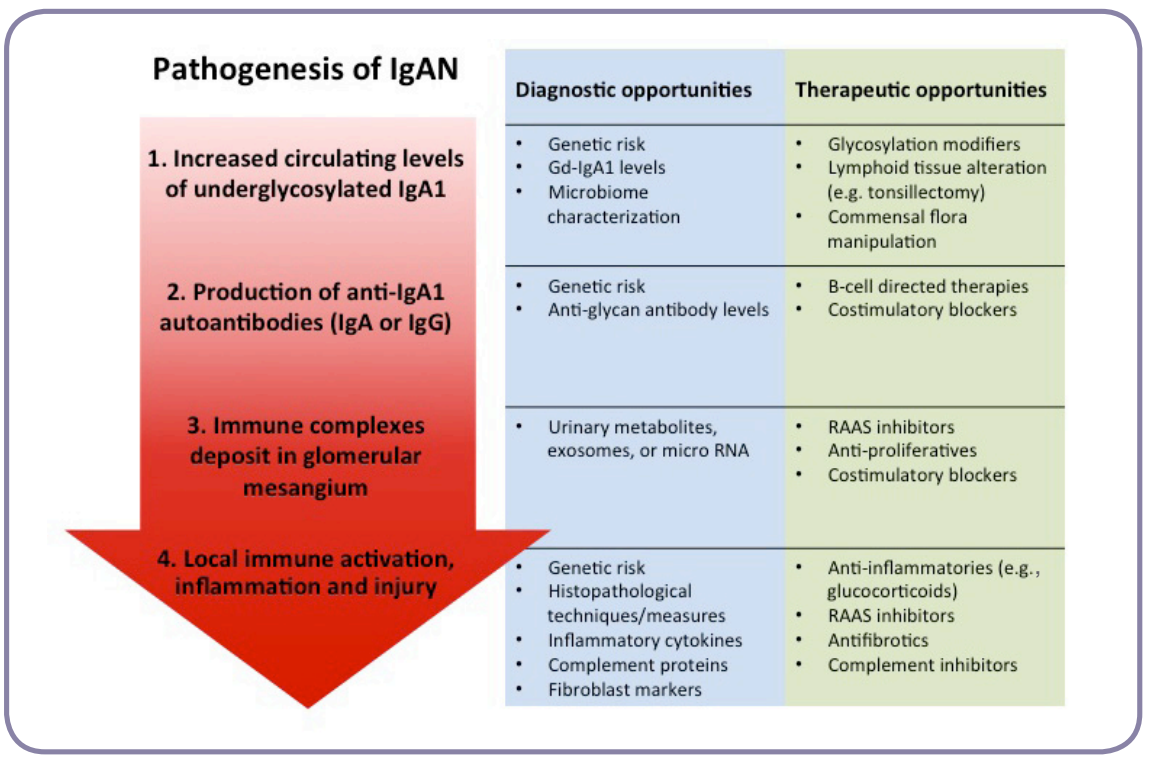
Because kidney biopsy remains the gold standard for IgAN diagnosis and an invaluable source of prognostic information, efforts continue to refine and augment the information gleaned from histopathology. A major advance was the development and publication of the Oxford classification of IgAN in 2009, involving four easily identified variables that were shown to predict clinical outcome in the inception cohort and to be reproducible among pathologists: mesangial cellularity (M), endocapillary proliferation (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T) (3). Subsequent to the publication of the Oxford classification, many reports have evaluated it in various cohorts. The largest was the recent publication from the pan-European VALIGA study, which confirms and generalizes the value of Oxford across a widely diverse group of patients representing the entire (European) spectrum of IgAN patients undergoing biopsy (4). VALIGA and several other studies have identified the "E" component as the least predictive of prognosis, but this interpretation is confounded because of the diffusion (expanded use) of immunosuppressive treatment for IgAN, whereby "E" may indicate disease amenable to therapy rather than irreversible damage like fibrosis. Beyond traditional biopsy techniques, studies continue to identify novel histopathologic markers of prognosis in IgAN, including specific immune cells, complement components, and markers of inflammation or fibrosis. Although the majority are unlikely to become routine in practice, they inform our understanding of disease pathogenesis, and they identify potential therapeutic targets.

Among the most illuminating developments in IgAN is the increasingly thorough characterization of the genetic contributions to both disease establishment and severity. Although geographic and racial differences in disease prevalence have long been recognized, until recently it was still debated to what degree these were due to differences in disease ascertainment (e.g., due to diverse local biopsy practices) rather than biology. It is now clear that a substantial portion of disease risk is conferred genetically.

Within the past 5 years, a series of genomewide association studies have identified at least seven susceptibility loci for IgAN (5). Furthermore, in an elegant example of congruity between genetics and epidemiology, a comprehensive geospatial analysis of genetic risk led by colleagues at Columbia University demonstrated that changes in genetic risk closely paralleled disease prevalence across 85 populations worldwide (5). The genetic loci identified thus far comprise genes associated with innate immunity, adaptive immunity (with the strongest signals consistently seen in the *MHC* region), and the complement system. This last locus is particularly interesting, involving genes encoding complement factor H and its five related proteins (*CFHR1-5*), which regulate the alternative complement pathway. Mutations in the *CFH/CFHR* gene region have been associated with C3 glomerulopathy, raising the intriguing possibility of overlapping pathogenic mechanisms with this much rarer form of proliferative glomerulonephritis. Although complement activation is well recognized in IgAN, the relative importance of the different initiating pathways—classic, alternative, and lectin—remains unclear. A series of reports has demonstrated the prognostic significance of various complement components on biopsy, including mannose-binding lectin, C1q, C4d, C3a, and C5a, and both mesangial and serum C3. These indicate that complement activation in IgAN may be a promising target for therapy.

What developments in IgAN can we expect in the near future? First, the number of genetic loci associated with the disease will undoubtedly expand as results from larger and higher-resolution genomewide studies are published. Large-scale,

Figure 1. Left, stepwise schematic of the pathogenesis of IgAN. Adjacent to each step are listed relevant opportunities for diagnosis or therapy. RAAS, renin-angiotensin aldosterone system.



longitudinal cohort studies are needed to validate proposed biomarkers and discover new ones; one notable example is the CureGN study, recently funded by the National Institutes of Health, an ambitious undertaking that will enroll patients with various glomerular diseases, including 600 patients with IgAN. The results from ongoing randomized controlled treatment trials are eagerly awaited, in particular the nearly completed German STOP-IgAN study, which examines the effects of immunosuppression versus supportive care, stratified by estimated GFR. Finally, we can expect to see novel immunosuppressive approaches tested in patients, targeting pathways across the disease pathogenesis including B-cell immunity, antibody generation, complement activation, inflammation, and fibrosis (Figure 1). Given the progress achieved thus far, both nephrologists and their patients have ample reason to be excited.

Pietro A. Canetta, MD, is assistant professor of medicine, division of nephrology, Columbia University College of Physicians and Surgeons, New York.

References

1. Mestecky J, et al. IgA nephropathy: molecular mechanisms of the disease. *Annu Rev Pathol* 2013; 8:217–240.
2. Suzuki Y, et al. Serum levels of galactose-deficient immunoglobulin (Ig) A1 and related immune complex are associated with disease activity of IgA nephropathy. *Clin Exp Nephrol* 2014 Jan 30 [Epub ahead of print].
3. Cattran DC, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009; 76:534–545.
4. Coppo R, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int* 2014 Apr 2 [Epub ahead of print].
5. Kiryluk K, et al. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. *Annu Rev Med* 2013; 64:339–356.
6. Kiryluk K, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet* 2012; 8:e1002765.