REVIEW ARTICLE

Immunoglobulin A nephropathy: current progress and future directions

CHUNLEI ZHANG, XUEHUI ZENG, ZHONGXIN LI, ZHE WANG, and SHUNMIN LI

SHENZHEN, CHINA AND HOUSTON, TEX

Immunoglobulin A (IgA) nephropathy is the most prevalent form of primary glomerulonephritis that often leads to end-stage kidney failure, thereby representing a major health challenge worldwide. Tremendous effort has been dedicated to the diagnosis, monitoring, and treatment of the disease, and the past several years have witnessed exciting advances that have enriched our understanding of the biology, etiology, and pathology of IgA nephropathy. The disease is characterized by predominant deposition of IgA immune complexes that progressively causes activation of mesangial cells, glomerular inflammation, and ultimately renal injury. Multiple recent independent high-throughput studies in cohorts have identified key susceptibility alleles, such as the major histocompatibility complex loci that are significantly associated with the risk of disease occurrence. Notably, a fraction of these risk loci encode proteins that participate in immune defense against mucosal pathogens, particularly intestinal nematodes, indicating a linkage between IgA-mediated antihelminth immunity and the pathogenesis of IgA nephropathy. The emerging "omics" technology also allows for systemic analysis of urinary and serum samples as a noninvasive procedure for diagnosis and prognosis, as demonstrated by several studies implicating the proteomic signature and microRNA profile as promising diagnostic and prognostic parameters. In the clinic, the current treatment protocol relies on suppression of the renin-angiotensin system to control blood pressure and proteinuria. This review scrutinizes and summarizes recent relevant findings that aim to translate researchers' benchside knowledge of disease initiation and development into patients' bedside diagnosis and therapy. (Translational Research 2015;166:134–144)

Abbreviations: BCL10 = B-cell CLL and lymphoma 10; C1GALT1 = core 1 β13-galactosyltransferase 1; CARD9 = Caspase Recruitment Domain Family, Member 9; ECM = extracellular matrix; GalNAc = N-acetylgalactosamine; GFR = glomerular filtration rate; HLA = human leukocyte antigen; MALT1 = mucosa associated lymphoid tissue lymphoma translocation gene 1; MBL = mannose-binding lectin; NO = nitrix oxide; TNF = tumor necrosis factor

From the Laboratory of Science Department, Shenzhen Affiliated Hospital, Guangzhou University of Traditional Chinese Medicine, Shenzhen, China; Department of Nephrology, Shenzhen Affiliated Hospital, Guangzhou University of Traditional Chinese Medicine, Shenzhen, China; Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Tex.

Submitted for publication November 26, 2014; revision submitted February 25, 2015; accepted for publication February 26, 2015.

Reprint requests: Shunmin Li, Department of Nephrology, Shenzhen Affiliated Hospital, Guangzhou University of Traditional Chinese Medicine, Shenzhen 518031, China; e-mail: Nephro.TCM@gmail.com.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.02.007

INTRODUCTION

Initially identified more than 4 decades ago, immunoglobulin A (IgA) nephropathy is now implicated as the most common cause of primary glomerulonephritis worldwide. The prevalence of the disease among distinct ethnic groups varies considerably, accounting for a large percentage of glomerular disease in Asian populations but significantly less in African groups.[1] Nearly 50% of patients with biopsy-confirmed IgA nephropathy ultimately develop end-stage renal disease, and the remaining experience remission or persistent low-grade hematuria or proteinuria.[2] To better predict the risk of clinical progression, the Oxford Classification is proposed to standardize the histology description and to minimize the observer-introduced variation. In this classification scheme derived from a large cohort of retrospective clinical data, 4 independent pathologic variables appear to be consistent and robust prognostic predictors, including mesangial hypercellularity score, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy and interstitial fibrosis.[3,4] The spectrum of the clinical manifestation of IgA nephropathy is expansive, ranging from sustained asymptomatic microscopic hematuria to gross hematuria during an upper respiratory or gastrointestinal infection. It has been established that some clinical parameters are strong indicators of severe disease progression, such as increased serum creatinine concentration (reduced glomerular filtration rate), hypertension, and severe proteinuria (protein excretion excessive of 1 g per day).

The pathogenic mechanisms by which IgA nephropathy occurs remain largely elusive. Previous studies have implicated mesangial deposit of IgA-dominant immune complexes as the defining hallmark of the disease. However, no correlation between the amount of IgA deposit and the extent of renal injury is established. Notably, the excessive IgA deposition alone is not sufficient to distinguish IgA nephropathy from other similar IgA-relevant disorders, such as Henoch-Schonlein purpura with nephritis.[5] Henoch-Schonlein purpura with nephritis is a type of systemic IgA-induced vasculitis that affects the skin, joints, and gut, in addition to the kidneys.[5] Therefore, understanding aberrant deposition of the pathogenic IgA at the molecular level holds therapeutic promise for treating IgA nephropathy and other IgA-mediated disorders alike. In this review, we scrutinize and summarize recent findings that provide novel insights into the development and progression of the disease. In particular, we highlight novel advances that improve the clinical diagnosis and intervention, which may offer clinical benefits to the patients.

PATHOGENESIS

Formation of IgA immune complex. Among the many pathologic features of IgA nephropathy (Fig 1), the defining hallmark is the glomerular accumulation of IgA immune complexes, which comprise exclusively the IgA1 subtype. Notably, the major pathogenic form of IgA1 seems to be predominantly polymeric, consisting of aggregates of monomeric or dimeric IgA, IgA-antigen immunocomplexes, or other protein components.[6] This is supported by multiple previous studies that demonstrate enhanced activation of human mesangial cells by polymeric IgA1 when compared with monomeric IgA1.[7-9] The IgA1 molecules are post-translationally modified through synthesis of 3–6 *O*-linked glycans at the hinge region between the first and second constant-region of the heavy chains. It is now understood that such modification of the IgA1 molecules is dysregulated in patients with IgA nephropathy. In homeostatic conditions, the carbohydrate side chains of IgA1 exist in multiple variations, but all contain the core structure of *N*-acetylgalactosamine (GalNAc) with a β1,3-linked galactose in monosialylated and disialylated forms. In contrast, the pathogenic form of IgA1 in patients with IgA nephropathy is galactose deficient, which is characterized by terminal GalNAc or sialylated GalNAc. The cell type that produces galactose-deficient IgA1 remains to be conclusively defined, although some evidence implicates B cells of mucosal origin.[10]

The underlying molecular mechanisms leading to the aberrant underglycosylation of IgA1 remain largely controversial. Multiple lines of evidence indicate that there might be a cell-intrinsic defect resulting from the abnormal expression or function of critical proteins involved in generating *O*-glycans. For instance, core 1 β1,3-galactosyltransferase 1 (C1GALT1) and α-N-acetylgalactosaminide α-2,6-sialyltransferase 2 are 2 essential catalysts for synthesizing β-galactosylation and attaching sialic acid to GalNAc, respectively. Genetic polymorphisms in these 2 genes have been shown to influence IgA glycosylation and confer significant predisposition to IgA nephropathy in 2 large case-control cohort studies on Han Chinese and European populations.[11-13] In line with this, Epstein Barr virus–immortalized peripheral IgA1-producing cells from patients with IgA nephropathy showed compromised expression and function of C1GALT1 and enhanced activity of α-N-acetylgalactosaminide α-2,6-sialyltransferase 2 compared with healthy controls.[14] However, despite these findings supporting a cell-intrinsic deficiency in enzymes that mediate *O*-galactosylation, additional studies have shown otherwise. Buck et al demonstrated that the expression and activity of