

Research progress of IgA nephropathy markers

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Abstract: IgA nephropathy is one of the most common forms of primary glomerulonephritis, and its clinical presentation and prognosis vary greatly among individuals, so early identification of individuals at high risk of poor prognosis is crucial. Currently, the clinical predictors of IgAN include hypertension, proteinuria, glomerular filtration rate and Oxford pathological staging, which are non-specific, invasive and delayed. With further research into the pathogenesis of IgAN, some new, simpler and earlier biomarkers have been identified. In this paper, the role of cytokine, protein and nucleic acid markers in the diagnosis of IgA nephropathy is described in a comprehensive manner based on the pathogenesis of IgA nephropathy. It is expected that based on the pathogenesis of IgA nephropathy, more markers of IgA nephropathy will be discovered by studying the four-fold strike doctrine and other related doctrines to help detect subclinical disease activity, monitor disease progression and assess treatment.

Keywords: IgA nephropathy; Biomarkers; Clinical diagnosis; Protein; Glycosylation.

1. IgA nephropathy and clinical diagnosis

IgA nephropathy (IgA nephropathy), also known as Berger's disease, is a primary glomerular disease in which IgA or IgA-based immune complexes are predominantly deposited in the glomerular thylakoid region. IgA nephropathy is an immune complex-mediated glomerular disease, but its exact pathogenesis is unclear. Studies have shown that non-specific viral and other types of microbial infections are the most common triggers of IgA nephropathy, and suspected dietary antigens, such as casein, have been found in the glomeruli of patients with IgA nephropathy. In addition, various studies have shown that the deposition of circulating immune complexes in the glomerulus is an important factor in the development of the disease.

The main method of detecting IgA nephropathy is immunopathological examination, which is usually characterised by the presence of large or scattered coarse particles and, in some cases, IgA deposits in the walls of small blood vessels. It also produces non-specific pathological changes, mainly proliferative damage to the thylakoid membrane, with interstitial fibrosis, crescent formation, IgA deposition and tubular atrophy. Renal biopsy is the best indicator of diagnosis and treatment, but it is not a non-invasive test and it is clinically difficult to monitor the disease by repeated renal puncture. Therefore, there is an urgent need to explore biomarkers that correlate with diagnosis and assessment of outcome.

2. Overview of IgA nephropathy markers

Clinical predictors of renal prognosis in IgAN nephropathy, such as proteinuria, hypertension, reduced estimated glomerular filtration rate (eGFR) [4-6] and histological grading are well known. Numerous studies have shown that many biomarkers in serum and urine have been identified as markers to detect IgAN nephropathy, including cytokine analogues, protein analogues, and nucleic acid analogues. Examples include galactose-deficient IgA1, IgA/IgG autoantibodies against galactose-deficient IgA1 and soluble CD89-IgA complexes in serum, and soluble transferrin receptors, interleukin 6/epidermal growth factor, fractalkine, laminin G-like 3 peptide, κ -light chain and mannan-binding lectin in urine. Some of these biomarkers may represent the development of non-invasive diagnostic tests that will help to detect subclinical disease activity, monitor disease

progression, assess treatment while avoiding complications associated with renal biopsy and help to improve the outcome, prognosis and quality of life of patients with IgAN.

3. Protein classes

3.1 C1GalT1

C1GalT1 belongs to the class of nephropathy marker proteins and plays an important role in kidney development. In recent years, the role of IgA1 deficiency in IgAN has been widely recognised and therefore how it causes galactose deficiency has become a focus of research. An increasing number of studies have shown that genetic variation in C1GalT1 affects Gd-IgA1 levels in IgAN. However, whether the expression of β 1,3-galactosyltransferase (β 1,3Gal-T) is affected may provide insight into how Gd-IgA1 levels are controlled in IgAN. Common variants of C1GalT1 affect Gd-IgA1 levels in IgAN. Expression levels of C1GalT1 are significantly downregulated in IgAN patients and are negatively associated with higher Gd-IgA1 levels. Higher levels of the expression of C1GalT1 were only low in B cells of IgAN patients. It can be concluded that B lymphocytes play an important role in determining C1GalT1 mRNA levels, and C1GalT1 mRNA expression is closely related to IgAN, so C1GalT1 can be used as a marker to detect IgA nephropathy.

In addition, C1GalT1 plays an important role in regulating O-glycosylation and is an essential enzyme for the synthesis of the core 1 structure of mucin-type O-glycans. Further studies are necessary to explore the role of C1GalT1 and O-glycosylation and its molecular chaperone Cosmc and its interaction with different C1GalT1 targets (e.g. integrin β 1) in the clinical setting. C1GalT1 studies will help to improve the understanding of IgAN and find new ways to treat and prevent IgAN in the future.

3.2 Gd-IgA1

Abnormally glycosylated polymorphic IgA1 (Gd-IgA1) is a protein-based cytokine-like marker known as "nephrogenic IgA" and is a key pathogenic factor in IgAN [11, 12, 13, 14, 15]. It has been found that serum Gd-IgA1 levels are positively correlated with the degree of kidney injury, while alterations in gut microbes have been found to increase antigen load and epithelial TLR recognition, thereby promoting B-cell sorting and IgA overproduction. Therefore, impaired intestinal mucosal barrier function is closely related to the production of Gd-IgA1. It was confirmed that elevated expression of Gd-IgA1 and inflammatory factors in IgAN patients may be associated with impaired intestinal mucosal barrier in IgAN patients, which opens up new directions for improving therapeutic monitoring and determining prognosis of IgAN. In addition, serum Gd-IgA1 may provide a new method for the initial diagnosis and prognosis of IgAN in patients who cannot undergo renal tissue biopsy, and its application in the diagnosis of IgAN patients deserves further investigation. Anti-Gd-IgA1 antibodies, the products of which can be used as non-invasive tests for the diagnosis of IgAN, of which IgG anti-Gd-IgA1 antibodies are more valuable, and it was found that serum levels of IgG anti-Gd-IgA1 antibodies in IgAN patients correlated with 24h urine protein quantification and Lee's pathological staging, suggesting that IgG anti-Gd-IgA1 may be of interest in monitoring the clinical progression of IgAN patients. The now generally accepted "sequential four-part strike theory" suggests that the formation of IgA antibodies to the circulating immune complex Gd-IgA1 and IgG antibodies to Gd-IgA1 is also part of the pathogenesis of IgAN [19, 20, 21].

3.3 TFR

The transferrin receptor (TFR) is a protein-like cytokine-like marker that mediates the entry of iron-containing ferritin from outside the cell into the cell, is present on the surface of many cells, and is one of the major immune cell membrane molecules in IgAN. Based on TFR studies, researchers have derived the serum soluble transferrin receptor (sTFR) through the proteolytic action of cell

surface receptors.) Studies have demonstrated that both transferrin receptors and serum transferrin receptors have important diagnostic value in chronic renal failure (CRF) [22, 23].

4. Nucleic acids

miR-148b belongs to the miRNA class, which is a nucleic acid cytokine-like marker. abnormal expression of miR-148b can promote abnormal glycosylation of IgA1 in IgAN, suggesting that miR-148b may play an important role in the development of diabetes and nephropathy. Meanwhile, miR-148b has been found to play a balancing role in the proliferation and apoptosis of kidney cancer cells. Overall, miR-148b is an important monitoring indicator in the detection of kidney disease.

5. Complement system

Various complement bodies have been proposed as prognostic biomarkers for IgAN. Complement activation can typically occur through three different pathways. Complement activation plays a role in the pathogenesis of IgAN and of the three complement activation pathways, the alternative pathway and the lectin pathway are associated with IgAN. IgA1 activates both pathways in vitro and components of the pathway are present in thylakoid immunodeposits, including proprietary and factor H in the alternative pathway as well as mannan-binding lectin, mannan-binding lectin-associated serine proteases 1 and 2 and C4d in the lectin pathway. Regardless of which complement activation pathway is at play, the production of C5b triggers the terminal sequence that eventually forms C5b-9. Thylakoid deposition of this terminal pathway complete complex, also known as the membrane attack complex, is commonly observed in IgAN. In patients with IgAN, the soluble form of this complex is elevated in the urine.

In addition, complement factors and their fragments can be used as biomarkers of IgA nephropathy in serum, urine or renal tissue. A better understanding of the role of complement in IgA nephropathy may provide potential targets and rationale for the development of complement-targeted therapies for this disease.

C3 plays a central role in complement activity, with its proteolytic cleavage first producing C3a and C3b, followed by C3b inactivation to produce iC3b (both C3 α and C3 β), which undergoes further catabolism to produce C3c and the terminal catabolic fragment C3dg. IgA-based deposition in the thylakoid region has been used as a diagnostic criterion for IgAN, and concomitant C3 deposition is common in patients with IgAN. However, the impact of complement activation on disease progression and prognosis is unclear. Activation of the alternative complement pathway and lectin pathway has been reported to be associated with the pathogenesis of IgAN. A Korean study showed that decreased circulating C3 levels were positively correlated with the intensity of C3 deposition in the glomerular thylakoid region and were a risk factor for progression to end-stage renal disease (ESRD). In several Asian studies, a high serum IgA:C3 ratio was associated with disease progression in IgAN.

6. Cytokines

6.1 TGF- β 1

TGF- β 1 is a multifunctional cytokine discovered by DeLarco and Todaro in 1978 from cells transformed by mouse sarcoma virus. The development of IgA nephropathy is accompanied by glomerulosclerosis, tubular atrophy and the development of interstitial fibrosis. These fibrotic changes and extracellular matrix accumulation are known to be stimulated by TGF- β 1. Induction of extracellular matrix components via TGF- β promotes wound healing. However, overexpression of TGF- β may lead to tissue overdeposition of extracellular matrix proteins, which ultimately leads to tissue fibrosis. increased expression of TGF- β mRNA and production of TGF- β protein is evident for various fibrotic kidney diseases, including IgA nephropathy.

It can be inferred that IgA aggregates increase the expression of TGF- β 1mRNA in cultured thylakoid cells. the study of TGF- β contributes to the understanding of the natural course of human IgA nephropathy. TGF- β in the thylakoid membrane correlates with the extent of extracellular matrix accumulation, and its increased gene expression from circulating CD4+ T cells may also contribute to glomerulosclerosis in patients with IgA nephropathy. Although TGF- β plays an important role in the pathogenesis of IgA nephropathy, it is not clear whether TGF- β mRNA expression in glomeruli is associated with clinical features and pathological findings.

6.2 Interleukin (IL)-6

The interleukin (IL)-6 family of cytokines is a group of cytokines consisting of IL-6, IL-11, ciliary neurotrophic factor (CNTF), leukaemia inhibitory factor (LIF), inhibin M (OSM), cardiac atrophy factor 1 (CT-1), cardiac hormone-like cytokine (CLC) and IL-27 .IL-6 is thought to exhibit homeostatic The pathways activated by IL-6 are involved in the regulation of cell proliferation, survival, differentiation and changes in cellular metabolism. deviations in IL-6 levels or abnormal responses to IL-6 signalling are associated with a variety of autoimmune diseases, including IgA nephropathy (IgAN). IgAN is associated with increased plasma concentrations of IL-6 and increased plasma concentrations of aberrant galactosylated IgA1 immunoglobulin (Gd-IgA1), which is specifically recognized by autoantibodies and leads to the formation of circulating immune complexes (CIC) with nephrogenic potential, as CIC deposited in glomerular tract vessels induces tract cell proliferation and glomerular damage [33].

We thus found that IL-6 is involved in IgA nephropathy plaque disease by producing Gd-IgA1 and regulating thylakoid cell proliferation. In addition, IL-6 production can be enhanced by upper respiratory or gastrointestinal tract infections, in patients with IgAN, usually secondary to sarcoid haematuria.

7. Protease classes

7.1 MMP-9

Matrix metalloproteinase-9 (MMP-9) is a member of the new family of Mecin and is primarily an extracellular protease. Although all of these enzymes may be target-mixed and the catalogue of potential substrates largely overlaps, MMP-9 has recently emerged as a major and apparently unique player in brain physiology and pathology .MMP-9 is normally expressed at low levels in glomerular endothelial cells and visceral epithelial cells, as well as in renal tubular epithelial cells and vessel walls.MMP-9 is expressed in patients with IgA nephropathy expression was significantly increased in thylakoid proliferating glomeruli and interstitial vessel walls ($P<0.001$), but significantly decreased in sclerosing glomeruli and not significantly altered in tubules. TIMP-1 expression was not detected in normal renal tissue. TIMP-1 was only slightly expressed in interstitial proliferative glomeruli of patients with IgA nephropathy. TIMP-1 expression was significantly increased in some sclerosing glomeruli and was most prominent in the tubular mesangium ($P<0.01$), mainly in tubular epithelial cells, mesangial cells and vascular endothelial cells. TIMP-1 expression was significantly correlated with serum creatinine levels ($P<0.05$), tubulointerstitial fibrosis ($P<0.01$) and leukocyte tubulointerstitial infiltration levels ($P<0.01$). MMP-9 expression did not correlate with proteinuria but was negatively correlated with serum creatinine levels ($P<0.05$) .

7.2 7.2 MMP-7

Matrix metalloproteinase-7 (MMP-7) is a small protein hydrolase that secretes zinc and calcium endopeptidases. It degrades a variety of extracellular matrix substrates and other substrates and plays an important regulatory role in many human pathophysiological processes . High levels of urinary MMP-7 ($>3.9 \mu\text{g/g}$ creatinine) were associated with a 2.7-fold increased risk of IgAN progression. In predicting IgAN progression, urinary MMP-7 levels were superior to (C statistic, 0.78) urinary angiotensinogen levels (C statistic, 0.75), epidermal growth factor (C statistic, 0.75), kidney damage

molecule 1 (C statistic, 0.68) and serum galactose-deficient IgA1 levels (C statistic, 0.59). Adding urinary MMP-7 levels to models with clinical data at biopsy (estimated glomerular filtration rate, mean arterial blood pressure and proteinuria) and MEST-C scores significantly improved the C statistic from 0.79 to 0.85, improved the 3-year risk prediction of IgAN progression (from 0.84 to a C statistic of 0.90), and improved risk reclassification (no category net weight classification improvement, 0.60). The predictive performance of urinary MMP-7 levels, alone or in combination with clinical data, was consistent in an external validation set .

Aberrant expression of MMP-9, TIMP-1, and MMP-7 may contribute to the progression of IgA nephropathy. Urinary MMP-7 levels are an independent predictor of IgAN progression. Adding urinary MMP-7 levels to the MEST-C score and clinical data at the time of biopsy significantly improves the prediction of the risk of IgAN progression.

8. Summary

There are several biomarkers involved in the development and progression of IgAN through different pathways, which can, to some extent, assess the disease and prognosis of IgAN patients, including Gd-IgA1 and its specific antibody IgG, complement C3, C4, TGF- β 1, urinary miRNA, AOPPs, etc. However, the accuracy of prediction of some indicators is still debatable. The combined assessment of multiple markers may improve the accuracy, and the dynamic monitoring of biomarkers may also be useful in determining the efficacy and prognosis, but more studies are needed to confirm this, and clinical tests need to be further simplified to improve the applicability of clinical tests. In the meantime, more new predictors need to be discovered, and the prospect of non-invasive markers to determine severity and predict progression of disease for early intervention is highly promising

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