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New Insights into the Pathogenesis of IgA Nephropathy

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Key Words
Autoantibodies · Galactose deficiency · IgA nephropathy · Immune complexes · *O*-glycans

Abstract
Background: IgA nephropathy, a frequent cause of end-stage renal disease, is an autoimmune disease wherein immune complexes consisting of IgA1 with galactose-deficient *O*-glycans (autoantigen) and anti-glycan autoantibodies deposit in glomeruli and induce renal injury. Multiple genetic loci associated with disease risk have been identified. The prevalence of risk alleles varies geographically: it is the highest in eastern Asia and northern Europe, lower in other parts of Europe and North America, and the lowest in Africa. IgA nephropathy is diagnosed by the pathological assessment of a renal biopsy specimen. Currently, therapy is not disease targeted but rather focused on maintaining control of blood pressure and proteinuria, ideally with suppression of angiotensin II. Possible additional approaches differ between countries. Disease-specific therapy as well as new tools for the diagnosis, prognosis, and assessment of responses to therapy are needed. ***Summary:*** Glycosylation pathways associated with aberrant *O*-glycosylation of IgA1 and, thus, production of autoantigen, have been identified. Furthermore, unique characteristics of the autoantibodies in IgA nephropathy have been uncovered. Many of these biochemical features are shared by patients with IgA nephropathy and Henoch-Schönlein purpura nephritis, suggesting that the two diseases may represent opposite ends of a spectrum of a disease process. Understanding the molecular mechanisms involved in the formation of pathogenic IgA1-containing immune complexes will enable the development of disease-specific therapies as well as diagnostic and prognostic biomarkers. ***Key Messages:*** IgA nephropathy is an autoimmune disease caused by the glomerular deposition of nephritogenic circulating immune complexes consisting of galactose-deficient IgA1 (autoantigen) bound by anti-glycan autoantibodies. A better understanding of the multi-step process of the pathogenesis of IgA nephropathy and the genetic and environmental contributing factors will lead to the development of biomarkers to identify patients with progressive disease who would benefit from a future disease-specific therapy.

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Introduction

IgA nephropathy is the most common primary glomerulonephritis in the world [1–3]. This disease is characterized by IgA-containing immune deposits in the glomerular mesangium and was initially described by Berger and Hinglais in 1968 [4] as a new entity based on the observation of 'intercapillary deposits of IgA-IgG' in renal biopsy specimens from patients presenting with microscopic hematuria and proteinuria. Subsequently, it was established that the IgA in the deposits is exclusively of the IgA1 subclass [5].

IgA nephropathy is diagnosed by the examination of renal cortical tissue based on the detection of IgA as the dominant or co-dominant immunoglobulin; the deposits are predominantly in the mesangium. Complement component C3 is usually found in the same distribution and is commonly accompanied by IgG, IgM, or both, although often with a lesser intensity (for reviews, see [3, 6]). Up to 60% of renal biopsy specimens from patients with IgA nephropathy have IgG co-deposits. In a minority of patients, IgA is the sole immunoglobulin detected. Light microscopy typically shows mesangial proliferation and expansion of the extracellular matrix [6]. Glomerular sclerosis and interstitial fibrosis are associated with progressive disease that leads to renal insufficiency.

The initial signs of IgA nephropathy frequently manifest in adolescence and young adulthood. Asymptomatic proteinuria and hematuria are common clinical presentations [3]. Painless macroscopic hematuria is frequent in children and adolescents and often coincides with mucosal infections, particularly those of the upper respiratory tract and/or digestive system. Disease incidence varies greatly by geographical location [3]. IgA nephropathy is found in up to 40% of native kidney biopsies in eastern Asia, but in less than 5% of such biopsies in central Africa [3, 7]. Notably, in some regions of the southeastern United States, African-Americans may be affected at the same rate as Caucasians [8, 9]. IgA nephropathy more often affects male than female Caucasians (ratio: 2–3:1) but affects both genders equally in eastern Asia. Although some of this geographic variability in disease incidence may be due to differences in thresholds or criteria for performing the diagnostic renal biopsy, genetically determined influences on the pathogenesis of the disease are thought to also play a significant role [10].

In most western countries there is no nationwide screening program for kidney disease. Thus, the discovery of kidney disease that merits a kidney biopsy depends on several factors that do not apply uniformly to all segments of the populations, most importantly the availability and cost of health insurance. Furthermore, some patients with mild disease and their physicians elect not to proceed with an invasive procedure with risks or prefer not to establish a diagnosis of kidney disease that may raise the cost of health, disability, or life insurance. By contrast, in Japan an annual medical checkup system in schools and workplaces was established by law. Individuals found to have proteinuria, with or without microscopic hematuria, are encouraged to consult a nephrologist. This practice undoubtedly contributes to the 10,000 native kidney biopsies performed in Japan each year. About 30–40% of these patients have IgA nephropathy. Thus, many Japanese patients are diagnosed at early stages of the disease that might not be discovered in western countries.

The immunohistological features of IgA nephropathy are similar to those of Henoch-Schönlein purpura nephritis [11, 12]. IgA nephropathy likely represents one end of a spectrum of an IgA1-induced disease process that leads to organ damage due to deposition (or in situ formation) of immune deposits generated by the binding of anti-glycan antibodies to galactose-deficient IgA1 (Gd-IgA1). The manifestation of the disease in patients with IgA nephropathy is generally restricted to the kidneys (rarely, patients also have IgA deposits in the walls of dermal capillaries). In contrast, Henoch-Schönlein purpura is an acute multi-organ disorder characterized by IgA1-mediated vasculitis involving the small vessels of the skin, gastrointestinal tract, kidneys, joints, and, rarely, lungs and central nervous system. Injury from such immune complexes can cause pneumonitis, bleeding from the gastrointestinal tract, arthritis/arthralgia, and purpura. Many patients have contracted a mucosal infection, especially in the upper respiratory tract, about 1–2 weeks before the appearance of the purpura. There is no laboratory test unique for Henoch-Schönlein purpura. Rather, the diagnosis is based on the combination of signs and symptoms, as very few other diseases cause the same syndrome. The disease typically affects children for whom it often exhibits a self-limited and benign course. In contrast, Henoch-Schönlein purpura in adults is associated with worse clinical features and outcome because of a higher prevalence of renal involvement.

Pathogenesis

Hypothesis on the Pathogenesis of IgA Nephropathy

The understanding of the pathogenesis of IgA nephropathy has evolved since 1968, when IgA nephropa-

thy was described as an IgA-IgG immune complex disease. Progress in technology and the development of new tools led to the definition of IgA nephropathy as an autoimmune disease with a multi-hit pathogenetic process (fig. 1). Specifically, Gd-IgA1 produced in elevated amounts in patients with IgA nephropathy (hit 1) is recognized in the circulation by unique autoantibodies (hit 2). The result is the formation of pathogenic immune complexes (hit 3), some of which ultimately deposit in the glomerular mesangium and induce renal injury (hit 4) [13]. Notably, serum levels of Gd-IgA1 as well as IgG and/or IgA autoantibodies specific for Gd-IgA1 correlate with disease severity and may predict disease progression, lending further support to this hypothesis [14–16]. In the absence of either hit 1 or hit 2, no pathogenic complexes can be formed (i.e., no hit 3 ensues). Thus, elucidating both hits is critical for understanding the disease processes that result in the formation of pathogenic immune complexes containing Gd-IgA1 as the key autoantigen.

Structure of IgA1 and Synthesis of IgA1 O-Glycans

IgA can form polymers, similarly as IgM, by binding the penultimate cysteine residue in a C-terminal 'tail' to a joining chain (J-chain) [17]. These J-chain-containing polymeric forms of IgA bind to the polymeric immunoglobulin receptor (pIgR) that mediates the transepithelial transport of external secretions. A part of pIgR, termed secretory component, remains attached to the secreted immunoglobulins. In humans, IgA is present in the circulation and external secretions in two subclasses, IgA1 and IgA2. Human circulatory IgA is mostly of the IgA1 subclass (~85% of total serum IgA) in its monomeric form [18]. The heavy chains of IgA1 and IgA2 exhibit a high degree of identity in the primary structure, but only IgA1 has *O*-glycans located in the unique hinge region between constant-region domains 1 and 2 of the heavy chain (CH1 and CH2) (fig. 2). The hinge region of IgA1 contains clustered *O*-glycans and is also a target of IgA1-specific proteases produced by several bacterial species, including human pathogens such as *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis,* and *Neisseria gonorrhoeae* [19]. IgA1 proteases cleave the IgA1 hinge region, usually at specific sites, and generate Fc and Fab fragments. These IgA1-specific proteases are an important virulence factor of pathogenic bacteria [19], and offer a unique tool for analyzing the site-specific heterogeneity of IgA1 *O*-glycans (for a review, see [20]).

Of the nine potential *O*-glycosylation sites in the hinge region of IgA1, usually three to six are glycosylated (fig. 2).

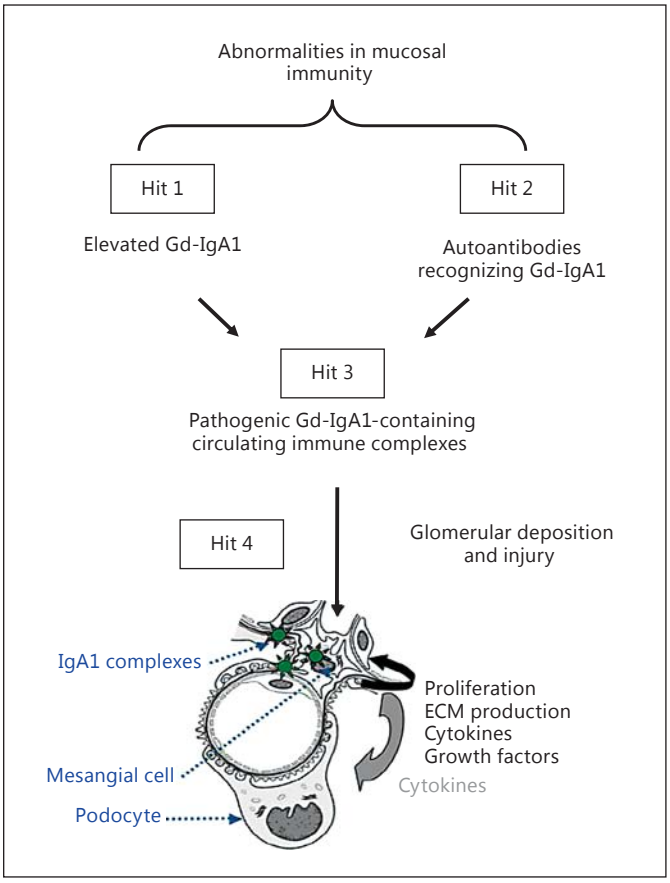

Fig. 1. Hypothesis on the pathogenesis of IgA nephropathy. Synthesis of IgA1 with some *O*-glycans deficient in galactose (autoantigen) is elevated. Gd-IgA1 is present in the circulation at increased levels (hit 1). This immunoglobulin is recognized by unique circulating anti-glycan autoantibodies (hit 2) [13, 14, 20]. This process results in the formation of pathogenic IgA1-containing circulating immune complexes (hit 3), some of which deposit in the glomeruli and induce renal injury (hit 4) [20]. Upstream factors are likely involved in abnormal mucosal immune responses characteristic for patients with IgA nephropathy [3]. An alternative hypothesis has been proposed to suggest that aberrantly glycosylated IgA1 accumulates in the mesangium as lanthanic deposits that are later bound by newly appearing autoantibodies, resulting in the in situ formation of immune complexes [92]. All hits and additional factors may be genetically regulated; 15 distinct genetic loci have been identified by genome-wide association studies to be associated with the risk of IgA nephropathy [7, 38]. It is certainly possible that other loci may influence the mechanisms of disease or the clinical expression of IgA nephropathy. ECM = Extracellular matrix.

In normal human serum IgA1, hinge-region glycoforms with four and five glycans are the most common (for a review, see [20]). Each heavy chain of IgA1 also contains two *N*-glycans, one in the CH2 domain (Asn263) and the second in the tailpiece portion (Asn459). The CH2 site

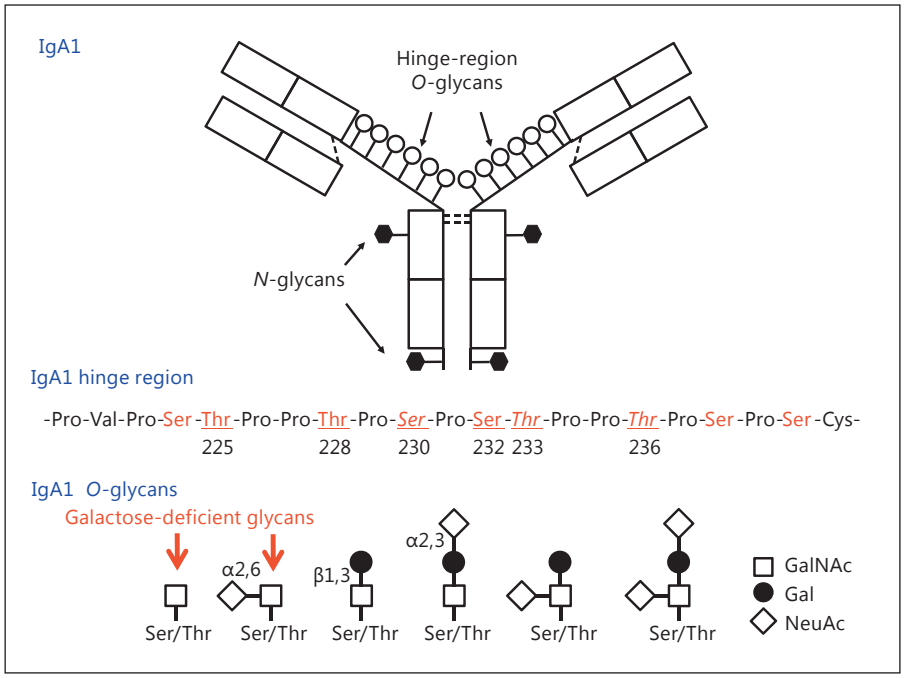

Fig. 2. Structure and *O*-glycosylation of human circulatory IgA1: monomeric IgA1 and hinge-region amino acid sequence with the sites of *O*-glycan attachment (top and middle panels). There are nine threonine and serine amino acids in the hinge region of monomeric IgA1 that can serve as the site for *O*-glycosylation (in red). Of these, usually up to six have an attached *O*-linked glycan (underlined and numbered in the amino acid sequence in the middle panel) in serum IgA1 [30]. The most common core 1 glycan consists of a disaccharide of GalNAc and galactose, with or without sialic acid. Serum levels of IgA1 with galactose-deficient glycans (red arrows in the bottom panel) are elevated in patients with IgA nephropathy. The sites most commonly found to have galactose-deficient glycans are shown in italics (S230, T233, T236 in the middle panel) [30]. See table 1 for details on glycoforms of normal serum IgA1.

contains a biantennary glycan that is usually not fucosylated, whereas the tailpiece site contains a fucosylated glycan [21, 22]. Normal human IgA1 in the circulation has core 1 *O*-glycans consisting of *N*-acetylgalactosamine (GalNAc) with β1,3-linked galactose. One or both saccharides can be sialylated: galactose with α2,3-linked and GalNAc with α2,6-linked sialic acid. The carbohydrate composition of the *O*-linked glycans on normal serum IgA1 is variable and the prevailing forms include the GalNAc-galactose disaccharide and its mono- and disialylated forms (fig. 2) [23–26]. Normal serum IgA1 had been thought to contain little or no galactose-deficient *O*-glycans [26], but recent findings indicate that some terminal or sialylated GalNAc is likely present (table 1).

The initiation of *O*-glycosylation of the hinge region of IgA1 had been originally attributed to the ubiquitously expressed GalNAc transferase T2 (GalNAc-T2), but more recently it has been shown that other GalNAc-Ts, including GalNAc-T1, GalNAc-T11, and GalNAc-T14, can also initiate *O*-glycosylation of the IgA1 hinge-region peptide (for a review, see [27]). After GalNAc attachment, the biosynthesis of *O*-glycans continues in a stepwise manner. The processing starts with the formation of the core 1 disaccharide structure, GalNAc-β1,3-galactose. This reaction is catalyzed by a β1,3-galactosyltransferase (C1GalT1). The expression of active C1GalT1 in the Golgi apparatus depends on a specific chaperone (Cosmc). Core 1 structures are modified by attaching sialic acid from CMP-*N*-acetylneuraminic acid (CMP-NeuAc) to galactose residues in a reaction catalyzed by Galβ1,3GalNAc α2,3-sialyltransferase (ST3Gal) and/or by attaching sialic acid to GalNAc residues catalyzed by an α2,6-sialyltransferase-II (ST6GalNAc-II). Notably, the premature sialylation of terminal GalNAc of IgA1 by ST6GalNAc-II would block other modifications, including galactosylation [28, 29].

Aberrant Glycosylation of IgA1 in IgA Nephropathy

Some galactose-deficient *O*-glycans may be present in normal IgA1 [30]. Extensive glycosylation analyses revealed aberrancies of IgA1 in patients with IgA nephropathy: most patients have elevated serum levels of Gd-IgA1, i.e., IgA1, with some *O*-glycans deficient in galactose [31–36]. Specifically, a fraction of circulatory IgA1 molecules has some hinge-region *O*-glycans without galactose, i.e., consisting of terminal or sialylated GalNAc (fig. 2). This galactosylation defect appears to be specific for IgA1, as other *O*-glycosylated serum proteins such as C1 inhibitor and IgD do not exhibit galactose deficiency [33, 37]. Genetic influences on the development and expression of IgA nephropathy have been recognized, and risk alleles of multiple genomic loci have been recently identified (for reviews, see [7, 38]). Notably, serum levels of Gd-IgA1 are genetically determined [8, 39, 40].

Table 1. Heterogeneity of desialylated *O*-glycans in normal human serum IgA1

	Site-specific microheterogeneity of desialylated IgA1 hinge-region *O*-glycans					
	T225	T228	S230	S232	T233	T236
Ser/Thr only	<1%	0%	1/10	0%	>1/2	>1/2
-□	<1%	1%	1/3	<1%	<1/4	1/4
-□●	Predominant	Predominant	1/2	Predominant	1/4	<1/4
	T P P 225	T P 228	S P 230	S 232	T P P 233	T 236

Data are derived from high-resolution mass spectrometric analyses. Sites S230, T233, and T236 are the primary sites of galactose deficiency in normal serum IgA1 and variable positional isomers. Modified from [24, 34]. White squares = GalNAc; black circles = galactose.

Humans produce ~70 mg of IgA per day per kg of body weight [18, 41]. Most IgA is produced in mucosal tissues, e.g., the gut, as polymeric IgA that is then selectively transported by a pIgR-mediated pathway into external secretions; only a small fraction of polymeric IgA enters the circulation [41]. IgA in the circulation, mostly IgA1, originates from the bone marrow and, to a lesser degree, from the spleen and lymph nodes. IgA-producing tonsillar cells may contribute to serum IgA and have been considered to play a role in the pathogenesis of IgA nephropathy [42–46]. IgA is catabolized predominantly in the liver by hepatocytes; the half-life of IgA in the circulation is about 5 days [47–51].

Analytical Approaches to IgA1 O-Glycosylation

Assessment of IgA1 *O*-glycosylation in IgA nephropathy initially utilized monosaccharide compositional analysis and *O*-glycan-specific lectins [32, 35, 52] and later developed into a quantitative lectin ELISA [34, 53, 54]. To characterize *O*-glycosylation of IgA1 at a molecular level, mass spectrometric analyses have been applied [55–61]. Direct localization of the attachment sites of *O*-glycan on IgA1 is allowed by combining a gentle fragmentation of hinge-region glycopeptides (electron-capture or electron-transfer dissociation) with high-resolution mass spectrometry [30, 62–65]. Individual glycoforms have been identified by their molecular masses and sites of *O*-glycan attachment. There are multiple *O*-glycoform isomers, i.e., hinge-region glycopeptides with the same number of glycans but with some attached at different sites [30]. These techniques also revealed significant heterogeneity of *O*-glycans of IgA1 in the circulation of healthy controls (table 1), but it remains to be determined precisely which IgA1 glycoform(s) in patients with IgA nephropathy is associated with disease expression and/or prognosis.

Autoantibodies Specific for Gd-IgA1 in IgA Nephropathy

Circulatory autoantibodies (IgG and/or IgA) bind to Gd-IgA1 and drive the formation of large-molecular-mass pathogenic immune complexes [66]. Better understanding of the nature of these autoantibodies came from studies of EBV-immortalized lymphocytes from patients with IgA nephropathy that were used for cloning cell lines producing IgG specific for Gd-IgA1 [14]. IgG secreted by these cells bound Gd-IgA1 in a glycan-dependent manner. Experiments using enzymatically modified Gd-IgA1 revealed that terminal GalNAc is required for autoantibody binding, whereas the addition of galactose or sialic acid blocked binding. Subsequent analyses of the cloned heavy- and light-chain antigen-binding domains of these IgG autoantibodies specific for Gd-IgA1 identified unique features in complementarity-determining region (CDR) 3 of the heavy chains. Specifically, the amino acid in the third position in CDR3 was S in 6 of 7 patients with IgA nephropathy (first four amino acids: YCSR/K), whereas healthy controls had A in that position (first four amino acids: YCAR/K) [14]. Additional experiments with recombinant IgG from these autoantibodies revealed that S in the third position in CDR3 of the heavy chains is necessary for efficient binding of IgG to Gd-IgA1. Currently, it is unknown whether this alteration (S vs. A in CDR3) originates from a genetic variation or a somatic mutation during an active immune response. Several observations suggest that the serum level of these autoantibodies rep-

resents a marker of disease activity as well as disease progression [14, 15]. If this finding is confirmed, this biomarker would be useful in assessing the response to treatment or selecting patients who would be at risk of progressive IgA nephropathy.

Formation of Pathogenic Immune Complexes and Activation of Mesangial Cells

Gd-IgA1 is recognized by unique circulating anti-glycan autoantibodies, thus driving a process leading to the formation of pathogenic immune complexes. These complexes activate mesangial cells in vitro, inducing cellular proliferation and overproduction of extracellular matrix components and cytokines/chemokines. IgA1 must be within an immune complex to activate mesangial cell proliferation; uncomplexed Gd-IgA1 does not stimulate the proliferation of mesangial cells [67–69]. Additional components from serum need to be present to form stimulatory complexes [67]. Complement likely plays a role in the formation and activities of these complexes (for a review, see [70]). The receptors engaged by pathogenic IgA1-containing immune complexes on mesangial cells are not well understood. Several studies identified transferrin receptor (CD71) as a key receptor for binding Gd-IgA1 (for reviews, see [71–73]).

An alternative hypothesis for the formation of IgA-containing complexes has been proposed, outlining a role of the soluble form of Fcα receptor (sCD89) that can generate complexes with Gd-IgA1 (for a review, see [71]). Notably, an association between the levels of sCD89-IgA complexes in serum and the severity of IgA nephropathy has been observed [74]: patients with IgA nephropathy without a progressive clinical course had high levels of sCD89 in contrast to low levels of sCD89 in the disease progression group, suggesting that sCD89-pIgA complexes may be protective. In contrast, an animal model suggested that the interaction between Gd-IgA1, sCD89, transferrin receptor, and transglutaminase 2 in mesangial cells is needed for disease development [75]. These aspects require further studies to clarify all of the processes occurring in patients with IgA nephropathy and identify the major mechanisms of disease pathogenesis and progression.

Among the growth factors playing a role in mesangial cell proliferation, platelet-derived growth factors (PDGFs) are considered leading contenders for the pathogenesis of IgA nephropathy (for a review, see [76]). PDGFs are potent mitogens and chemoattractants for mesenchymal cells and play important roles in mesangioproliferative disease, particularly in IgA nephropathy. Once Gd-IgA1-containing immune complexes are deposited or formed in the mesangium, PDGFs may be synthesized and released by resident cells or infiltrating inflammatory cells. Of the five PDGF dimers (PDGF-AA, -AB, -BB, -CC, and -DD) and three dimeric PDGF receptors (PDGFRs) with tyrosine-kinase activity (PDGFR-αα, -αβ, and -ββ), PDGFR-β and its ligands PDGF-BB (and possibly -AB) and -DD are crucial mediators of mesangial cell proliferation. PDGF-BB and PDFGR-β are overexpressed in experimental mesangioproliferative nephritis and human IgA nephropathy and are related to the degree of glomerular proliferation and extent of interstitial fibrosis. The systemic administration of PDGF-BB or overexpression of PDGF-DD in podocytes of mice induces mesangioproliferative glomerulonephritis. Specific anti-PDGF therapy to neutralize PDGF-B or -D or blocking the PDGFR-β prevented the development of mesangial proliferation in this animal model (for a review, see [76]).

Pathogenesis of IgA Nephropathy and Henoch-Schönlein Purpura Nephritis

Multiple lines of evidence, including shared glycosylation abnormalities of IgA1, anti-Gd-IgA1 autoantibodies, and presence of IgA1-containing immune complexes in the circulation, have led to the postulate that the two diseases, IgA nephropathy and Henoch-Schönlein purpura nephritis, represent the opposite ends of a spectrum of a disease process (for a comprehensive comparison of all aspects of the two disorders, see table 1 in [3]). Multiple genetic loci with their risk alleles for the development IgA nephropathy have been identified that fit the multi-hit pathogenesis scheme (fig. 1). There has not been a similar genetic study for patients with Henoch-Schönlein purpura nephritis.

Implications for Diagnosis, Prognosis, and Treatment of IgA Nephropathy

Diagnosis and Prognosis

An elevated serum level of Gd-IgA1 is not sufficient to induce disease [13] and, thus, is unlikely to be suitable as a stand-alone biomarker for diagnosis. However, a combination of markers, such as Gd-IgA1 and anti-glycan autoantibodies, shows more promise [77]. Also, urinary peptides may be of future interest for developing diagnostic and prognostic biomarkers relevant to IgA nephropathy. Such markers may be developed, for example, using urinary peptidomics [78–82].

Table 2. Potential biomarkers and disease-specific approaches for the treatment of IgA nephropathy

Hit	Pathogenic process	Potential biomarkers	Disease-specific approaches to therapy
1	Elevated synthesis of Gd-IgA1	Serum level of Gd-IgA1 by lectin ELISA and/or mass spectrometric profiling	Reduce Gd-IgA1 production – Manipulate enzyme expression in IgA1-producing cells – Reduce number of Gd-IgA1-producing cells
2	Production of autoantibodies binding to Gd-IgA1	Serum anti-glycan antibodies	Reduce production of Gd-IgA1-specific autoantibodies – Depletion of antigen-specific cells – Block affinity maturation to reduce affinity for Gd-IgA1 – Depletion of autoantibody from circulation
3	Formation of pathogenic Gd-IgA1-containing immune complexes	Circulating immune complexes and their specific components	Blockade of immune-complex formation – Block epitopes of autoantigen (Gd-IgA1) by non-crosslinking antibodies – Block autoantibodies by an epitope-containing glycopeptide or glycomimetic – Block activation of complement
4	Glomerular deposition and injury	Urinary immune complexes or complement degradation products, or novel markers of glomerular injury	Blockade mesangial cell activation – Suppression of complement activation – Block binding of Gd-IgA1-containing immune complexes to mesangial cells – Block mesangial cell signaling induced by Gd-IgA1-containing immune complexes

The prognostic value of serum levels of Gd-IgA1, anti-glycan autoantibodies, or their combination needs to be assessed in future studies. Moreover, the heterogeneity of IgA1 galactosylation and/or the fine specificity of the autoantibodies have yet to be tested for an association with the clinical expression of disease or prognosis.

Treatment

There is no therapy that is based on disrupting or dampening disease-specific mechanisms in the pathogenesis of IgA nephropathy. The current approaches to treatment vary substantially between the western and eastern hemispheres. Recommendations and suggestions for the treatment in the western approach have been summarized in the KDIGO guidelines [83]. The primary emphasis entails efforts to control blood pressure and proteinuria (to <0.5 g/day) with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. For patients with proteinuria persistently greater than 1 g/day despite maximum tolerated doses of such agents and well-controlled blood pressure, two options have been suggested: (1) fish oil and (2) a 6-month course of glucocorticoids for the subset of patients with eGFR >50 ml/min/1.73 m^2. For patients with crescentic IgA nephropathy (defined as crescents in >50% of glomeruli) and a rapid deterioration in renal clearance function, treatment with glucocorticoids and cyclosporine (or azathioprine) is suggested. The use of immunosuppressive agents in patients with stable eGFR <30 ml/min/1.73 m^2, or mycophenolate, anti-platelet agents, or tonsillectomy in any setting is not supported.

The approach to therapy in the eastern hemisphere includes the suppression of angiotensin II for the treatment of proteinuria and hypertension. The use of tonsillectomy in the treatment armamentarium is favorably viewed in Japan, and the procedure is often combined with glucocorticoid therapy. Since tonsillectomy with pulse glucocorticoids was first reported in 2001 [84], numerous reports of uncontrolled studies in Japan have described benefits of such a therapy for preserving renal function and improving proteinuria and hematuria [85, 86]. The benefit may be limited to patients with preserved eGFR [45, 87]. A recent multicenter randomized controlled trial of tonsillectomy with pulse glucocorticoids found a greater effect to attenuate proteinuria compared to glucocorticoid pulse therapy alone, but there was no benefit for eGFR [88]. In China, the clinical remission rate was higher in patients with tonsillectomy than in those without [89]. The mechanism of benefit of tonsillectomy may include a reduction of serum levels of Gd-IgA1 and/or autoantibodies specific for Gd-IgA1.

Traditional Chinese medicine has been used for many years to treat patients with chronic kidney diseases, including IgA nephropathy, to decrease proteinuria and improve or stabilize renal clearance function. In the 1980s, kidney biopsy was widely accepted by many traditional Chinese medical facilities. New diagnostic criteria for several kidney diseases were developed by combining kidney biopsy results and traditional Chinese medical theory. The treatment of IgA nephropathy using traditional Chinese medicine has been applied under these

guidelines, although variations of diagnostic criteria exist due to differences in interpretation. *Tripterygium wilfordii* Hook F (thunder god vine), recognized recently as an immunosuppressive treatment, was widely used for patients with chronic kidney diseases to decrease proteinuria. This therapy has been associated with fewer side effects than the treatment with glucocorticoids and/or cytotoxic agents. Unfortunately, only a few of the results have been analyzed, summarized, and published. In 2010, one study examined the findings of four randomized clinical trials with a total of 188 IgA nephropathy patients [90]. Treatment with the herb significantly decreased nonnephrotic proteinuria and stabilized renal function [90]. For the current treatment of patients with IgA nephropathy, most regimens include a mixture of drugs. Some prescriptions are prepared by traditional Chinese pharmaceutical companies in the form of ready-to-use capsules or decoctions. One preparation, Shenle capsules with hirudo and other herbs, was tested in 36 non-nephrotic patients with IgA nephropathy; the therapeutic benefit for decreasing proteinuria was similar to that of fosinopril, an angiotensin-converting enzyme inhibitor [89]. The major active chemical components of the traditional medicine prescriptions and their pharmacological mechanisms remain unclear. In contrast, the biological effects of nephrokeli, a decoction with several herbal mixtures that has been used successfully for decades in China to treat IgA nephropathy patients, have been examined. Using the mixture in a rat model reduced the expression of sphingosine-1-phosphate receptor 2 or 3 in the kidney, and that effect correlated with less proliferation of mesangial cells [91].

While waiting for the clarification of the mechanisms responsible for the therapeutic benefit of tonsillectomy and traditional Chinese medications, it is now possible to envision novel approaches to disease-specific treatment based on the 4-hit hypothesis for the pathogenesis of IgA nephropathy (table 2). Disrupting the cascade of events at hit 1 and hit 2 (fig. 1) would prevent the formation of nephritogenic immune complexes [3, 13, 92] and will likely require the development of parenteral formulations of small biological molecules. Dampening the involvement of complement would attenuate the effects of hit 3 and hit 4. Repurposing some agents that interfere with cytokine pathways may reduce renal injury after nephritogenic immune complexes bind to mesangial cells (hit 4). The clinical development of disease-specific therapy is at least several years in the future.

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Disclosure Statement

The authors have nothing to disclose.

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