IgA nephropathy: the lectin pathway and implications for targeted therapy

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Jonathan Barratt[1], Richard A. Lafayette[2], Hong Zhang[3], Vladimir Tesar[4], Brad H. Rovin[5], James A. Tumlin[6], Heather N. Reich[7] and Jürgen Floege[8]

[1]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [2]Department of Medicine, Division of Nephrology, Stanford Health Care, Stanford, California, USA; [3]Renal Division, Department of Internal Medicine, Peking University Institute of Nephrology, Beijing, China; [4]Department of Nephrology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [5]Department of Internal Medicine, Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [6]Department of Medicine, Division of Renal Medicine, Emory University, Atlanta, Georgia, USA; [7]Department of Medicine, Division of Nephrology, University of Toronto and University Health Network, Toronto, Ontario, Canada; and [8]Department of Nephrology and Rheumatology, RWTH Aachen University Hospital, Aachen, Germany

Many patients with immunoglobulin A nephropathy (IgAN) progress to kidney failure even with optimal supportive care. An improved understanding of the pathophysiology of IgAN in recent years has led to the investigation of targeted therapies with acceptable tolerability that may address the underlying causes of IgAN or the pathogenesis of kidney injury. The complement system—particularly the lectin and alternative pathways of complement—has emerged as a key mediator of kidney injury in IgAN and a possible target for investigational therapy. This review will focus on the lectin pathway. The examination of kidney biopsies has consistently shown glomerular deposition of mannan-binding lectin (1 of 6 pattern-recognition molecules that activate the lectin pathway) together with IgA1 in up to 50% of patients with IgAN. Glomerular deposition of pattern-recognition molecules for the lectin pathway is associated with more severe glomerular damage and more severe proteinuria and hematuria. Emerging research suggests that the lectin pathway may also contribute to tubulointerstitial fibrosis in IgAN and that collectin-11 is a key mediator of this association. This review summarizes the growing scientific and clinical evidence supporting the role of the lectin pathway in IgAN and examines the possible therapeutic role of lectin pathway inhibition for these patients.

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Correspondence: *Jürgen Floege, Department of Nephrology and Rheumatology, RWTH Aachen University Hospital, Pauwelsstraße 30, 52057 Aachen, Germany. E-mail: jfloege@ukaachen.de*

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Immunoglobulin A nephropathy (IgAN) is the most commonly occurring glomerular disease, and many patients progress to kidney failure even with optimal supportive care and currently available therapy.[1,2] Patients with IgAN and persistent proteinuria (>0.75 g/d) have a high risk of progressive loss of kidney function.[3] Systemic corticosteroids may temporarily slow the progression of kidney disease in these patients, but the data are not consistent and toxicity remains an issue.[3] When possible, patients with persistent proteinuria should be considered for participation in a clinical trial, in the hopes of discovering safer, effective therapy.[3] There is clearly an unmet medical need for additional treatment options to slow or even reverse the loss of kidney function. An improved understanding of the pathophysiology of IgAN in recent years has led to the investigation of targeted therapies with acceptable tolerability that may address the underlying causes of IgAN or the downstream pathogenesis of kidney injury. Activation of the complement system—particularly through the lectin and alternative pathways—has emerged as a key mediator of kidney injury in IgAN, including potential contributions to tubulointerstitial fibrosis, and is an attractive target for investigational therapy. The role of the alternative pathway in the pathophysiology of IgAN has been reviewed extensively elsewhere.[4] Thus, this review focuses on the growing scientific and clinical evidence supporting the pathophysiologic role of the lectin pathway and the possible therapeutic role of lectin pathway inhibition in IgAN.

IgAN pathophysiology: kidney injury and the complement system

Recent research has elucidated many aspects of how IgAN develops and how it results in kidney injury, but there is still much that remains to be determined. A "four-hit" process has been postulated for IgAN pathophysiology.[5,6] The first hit is the generation (and increased systemic presence) of "mucosal type" poorly *O*-glycosylated galactose-deficient IgA1 (Gd-IgA1).[7–9] This Gd-IgA1 is believed to be predominantly generated by the intestinal mucosal-associated lymphoid tissue, which has been identified as a novel therapeutic target in IgAN.[10] The second hit is the formation of antiglycan IgA and

IgG autoantibodies recognizing Gd-IgA1.[11,12] In the third hit, Gd-IgA1 forms polymeric IgA1 immune complexes, with or without antiglycan autoantibodies.[13,14] The fourth hit involves the deposition of these complexes in the glomerular mesangium, activating (among other injury pathways) the complement system, which contributes to kidney inflammation and scarring.[4,15]

The complement system is a key component of innate and adaptive immunity that mediates inflammation and fibrosis, both systemically and locally in organs.[16–22] In the classical pathway, binding of the pattern-recognition molecule, C1q, to IgG or IgM antibodies or to immune complexes initiates a cascade of events starting with the activation of C2 and C4. In the lectin pathway, carbohydrates expressed on the surface of injured cells or pathogens bind to 1 of 6 pattern-recognition molecules: mannan-binding lectin (MBL), collectin-10, collectin-11, ficolin-1, ficolin-2, or ficolin-3.[23] These pattern-recognition molecules form complexes with MBL-associated serine proteases 1 (MASP-1) and 2 (MASP-2), which activate C2 and C4.[24,25]

In both the classical and lectin pathways, activated C2 and C4 combine generating a C3 convertase (C4b2b), which cleaves C3 to its active components. The activation of C3 can also occur in a C4-independent "bypass" manner[26]; MASP-2, when bound to a lectin pathway activation complex, has been shown to activate C3 directly in the absence of C4 or C2.[27] In addition to activating complement components, MASP-2 (when complexed with the pattern-recognition molecule MBL of the lectin pathway) also cleaves prothrombin to promote clot formation.[28]

Key evidence supporting the contribution of the alternative pathway to IgAN includes the presence of Factor B, Factor H, and Factor H–related proteins in kidney biopsies.[4] Factor H–related proteins appear to compete with Factor H, preventing it from deactivating C3b. The initial rate-limiting step of the alternative pathway is cleavage of Factor B by Factor D.[29] Mature Factor D is the result of proteolytic activation of its zymogen form, pro-Factor D, by MASP-3, initiating a cascade of proteolytic cleavages that lead to the alternative pathway C3 convertase (C3bBb).[29] This results in the activation of additional C3. MASP-3 may link the alternative and lectin pathways of complement; it is responsible for activating Factor D in the alternative pathway and also complexes with pattern-recognition molecules of the lectin pathway.[30,31] Patients with IgAN and progressive kidney disease, as compared with patients with stable kidney disease, have reduced plasma MASP-3, reduced glomerular deposition of Factor H, and increased glomerular deposition of Factor H–related proteins 1 and 5, consistent with plasma MASP-3 being consumed as a result of activation of the alternative pathway in patients with disease progression.[32]

In addition to amplifying responses to the classical and lectin pathways, the alternative pathway might be activated directly in IgAN. IgA1 deposits in the mesangium contain properdin, a key component of the alternative pathway.[33] *In vitro* and *in vivo* research has shown that properdin can act as a pattern-recognition molecule for injured tissues.[34,35] Other research has shown that properdin does not act as a pattern-recognition molecule to generate C3b but stabilizes existing C3b previously generated by the classical pathway, the lectin pathway, or by spontaneous tick-over of the alternative pathway.[36]

Once C3 is activated, all 3 pathways lead to the activation of C5 and then binding of C5b, 6, 7, 8, and 9, resulting in assembly of the "membrane attack complex" C5b–9. Intermediate products of the complement system (activated C3, C4, and C5) also contribute to the immune response through inflammation and stimulation of chemotaxis and phagocytosis. Compared with healthy individuals, patients with IgAN have increased mesangial deposition of C5b–9 and have been variably described to also have peripheral capillary loop, tubule basement membrane, and vascular C5b–9 deposition.[37] The intensity of glomerular staining for C5b–9 correlates with glomerular hypercellularity, glomerulosclerosis, interstitial inflammation, interstitial fibrosis, tubular atrophy, and disease progression in patients with IgAN.[37]

Several studies have examined urinary C5b–9 as a possible noninvasive biomarker for IgAN severity, with mixed results. Urinary C5b–9 is higher in patients with IgAN than in healthy subjects, and urinary C5b–9 is positively correlated with the extent of kidney damage in some studies[38–40] but not in others.[17,41,42] A fall in urinary C5b–9 has been reported to precede disease remission,[17] but baseline urinary C5b–9 does not independently predict estimated glomerular filtration rate decline or clinical response during treatment.[40]

Additional research is needed to confirm the relative contributions of each pathway to the activation of complement in patients with IgAN, whether particular subgroups of patients can be identified with more dominant activation of one pathway, and how this relates to outcomes (Figure 1, Table 1).[4,25,33,35,43–54] Additional key questions for future research include whether patterns of lectin pathway and alternative pathway activation change during the natural history of IgAN in an individual patient, or if the contributions of each pathway vary by patient-specific factors such as race, ethnicity, or age.

The lectin pathway and glomerular injury in IgAN

To examine the role of different complement pathways in glomerular injury in IgAN, numerous studies have examined the presence of complement components responsible for glomerular injury in mesangial deposits. The classical pathway is likely not involved in the glomerular changes observed in IgAN because mesangial deposition of C1q is observed in a minority (typically 0%–20%) of patients with IgAN.[43–45] In addition, C1q binds more strongly to IgG1 and IgG3 than it does to IgG2 or IgG4,[55] and IgG2 is the predominant subclass of IgG found in Gd-IgA1-containing immune complexes.[12] Alternative pathway activation is typically involved in glomerular injury in IgAN, based on the presence of activated C3, either with or without C1q or MBL co-deposition, in most kidney biopsies.[45,46]

Activation of the lectin pathway in glomerular injury in IgAN has been suggested by a series of studies in which

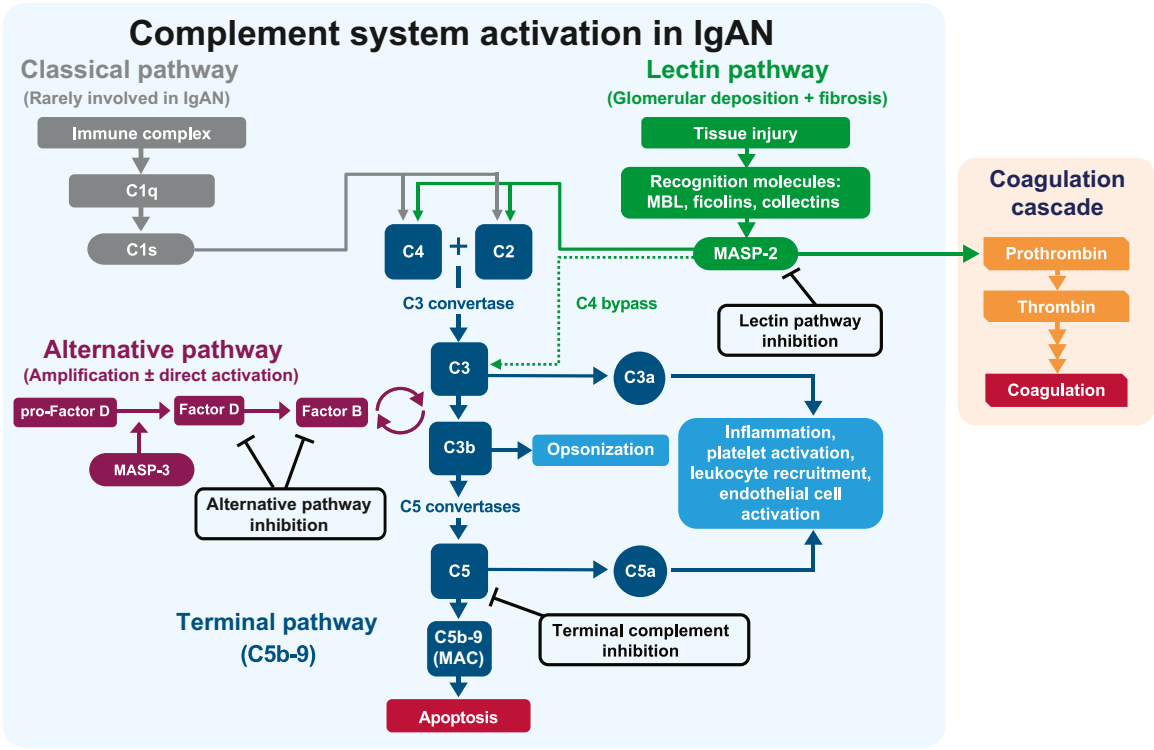

Figure 1 | Role of the complement system in the pathogenesis of immunoglobulin A nephropathy (IgAN). MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin. Adapted under the terms of the CC BY license from Gavriilaki E, Ho VT, Schwaeble W, et al. Role of the lectin pathway of complement in hematopoietic stem cell transplantation-associated endothelial injury and thrombotic microangiopathy. *Exp Hematol Oncol*. 2021;10:57.[25] https://doi.org/10.1186/s40164-021-00249-8

kidney biopsies from patients with IgAN consistently showed glomerular deposition of MBL (Figure 2)[46] together with IgA1 in up to 50% of patients (Table 1).[45–50] Mesangial IgA deposits from patients with IgAN that are MBL-positive usually contain other components of the lectin pathway including MASP-1, MASP-2, C4d, and C4-binding protein (Table 2).[45–50] The presence of these proteins in mesangial deposits supports the involvement of the lectin pathway in glomerular changes in IgAN. Additional support from *in vitro* studies shows that MBL binds to polymeric IgA complexes, similar to those generated in IgAN, activating the lectin pathway to cleave C3 and C4.[56]

To further explore the role of the lectin pathway in IgAN, several studies have examined relationships between MBL or ficolin glomerular deposition and disease severity or prognosis in IgAN. Glomerular deposition of these pattern-recognition molecules for the lectin pathway has been associated with more severe glomerular damage (mesangial proliferation, extracapillary proliferation, glomerular sclerosis, and interstitial infiltration) and more severe proteinuria and hematuria.[46,49,50] Compared with patients with MBL-negative glomeruli, patients with MBL-positive glomeruli are younger and have more rapidly progressing IgAN.[47] Patients with IgAN and genetic MBL deficiency, which is a relatively common immune deficiency, may also have a higher risk of IgAN disease progression, suggesting a U-shaped relationship between MBL and IgAN severity or progression[57–60]; however, this relationship is not evident for all MBL mutations.[61]

Table 1 | Key evidence for the role of the complement pathway in IgAN

Pathway	Key evidence
Classical	• Binding of IgG/IgM antibodies or immune complexes to C1q forms C1s, which activates C2 and C4, but mesangial deposition of C1q occurs in only 0% to 20% of patients with IgAN,[43–45] suggesting that the classical pathway is rarely involved in glomerular changes.
Lectin	• Carbohydrates on injured cells or pathogens bind to 1 of 6 pattern-recognition molecules: MBL, collectin-10, collectin-11, ficolin-1, ficolin-2, or ficolin-3. Up to 50% of patients with IgAN show glomerular deposition of MBL with IgA1.[45–50] • IgA1 immune complexes from patients with IgAN increase mesangial secretion of collectin-11, which deposits with IgA1 complexes on cell surfaces and initiates the activation of complement and deposition of C3.[51] • Deposition of collectin-11 activates MASP-2 and leads to inflammation, fibrosis, and tubular damage.[52–54]
Alternative	• Increased levels of Factor B, Factor H, or Factor H–related proteins are present in most kidney biopsies from patients with IgAN.[4] In addition to spontaneous tick-over of the alternative pathway and amplification of the lectin pathway,[35] mesangial deposition of properdin (a pattern-recognition molecule for the alternative pathway)[33] suggests that direct activation of the alternative pathway may occur in patients with IgAN.

IgAN, immunoglobulin A nephropathy; MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin.

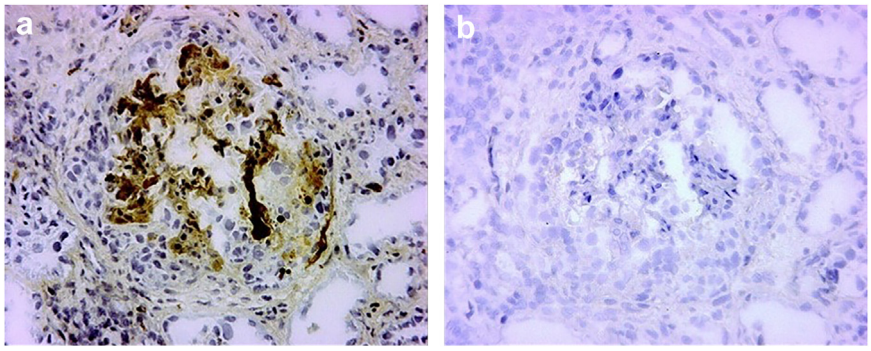

Figure 2 | Mesangial expression or deposition of mannan-binding lectin (MBL) in a patient with immunoglobulin A nephropathy. (**a**) Deposition of MBL in the glomeruli, shown as positive staning for a monoclonal antibody directed against MBL. (**b**) Negative staining of the glomeruli from the same patient, using an isotype control monoclonal antibody not directed against MBL. Adapted from Roos A, Rastaldi MP, Calvaresi N, et al. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *Journal of the American Society of Nephrology,* volume 17, issue 6, pages 1724–1734.[46] https://journals.lww.com/jasn/Fulltext/2006/06000/Glomerular_Activation_of_the_Lectin_Pathway_of.27.aspx Copyright © 2006 by the American Society of Nephrology. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

Additional evidence to support lectin pathway activation in glomerular injury is provided by C4d deposition in glomeruli, as the alternative pathway does not involve cleavage of C4. Studies in China and Europe have reported C4d deposition in the glomeruli of approximately 30% to 40% of patients with IgAN, with higher incidences among patients with kidney impairment or progressive kidney disease versus those with normal or stable kidney function (Table 3).[32,62–69] Several of these studies showed that mesangial deposition of C4d is independently associated with more rapid progression of kidney disease in IgAN.

MBL in urine and serum

Given the challenges of obtaining kidney biopsies in routine clinical practice, less invasive measurements of MBL levels in urine and serum were examined as possible biomarkers for disease severity and clinical outcomes. Elevated MBL in urine was associated with more severe glomerular injury in IgAN.[70] These findings are consistent with localized elevation of MBL in the kidney, in response to deposition of IgA1 immune complexes, and increased urinary MBL correlated with increased glomerular deposition of MBL.[49,70] Urinary MBL tends to increase with proteinuria, but variations in urinary MBL mostly depend on the presence of glomerular MBL deposits, and urinary MBL increases can occur in patients with low levels of proteinuria.[39] Although there is evidence that MBL in urine corresponds with MBL deposits in glomeruli, it remains to be determined whether elevated MBL in the urine is a biomarker for IgAN exacerbated by lectin

Table 2 | Glomerular deposition of MBL and other components of the lectin pathway in kidney biopsies from patients with IgAN

		Other evidence of lectin pathway activity in MBL-positive glomeruli[a]		
Study	**MBL, n/N (%)**	**MASP-1/2 (%)**	**Complement (%)**	**Comments**
Endo *et al.*[47]	11/45 (24)	MASP-1: 100	C3c + C5b-9: 100 C4c: 36	Of 11 MBL-positive: C1q, 9%; properdin, 55% Of 34 MBL-negative: MASP-1, 0%; C3c: 91%; C5b–9: 100%
Matsuda *et al.*[50]	7/42 (17)	–	C2: 43 C4: 29	Of 35 MBL-negative: C2: 6%; C4: 17%
Lhotta *et al.*[48]	3/11 (27)	–	–	MBL-positive patients had “rather advanced disease”
Hisano *et al.*[45]				
IgA1 alone	5/17 (29)	MASP-1: 0	C3c: 71 C4: 0	IgA2 may activate the lectin pathway in IgAN
IgA1 + IgA2	19/19 (100)	MASP-1: 100	C3c: 100 C4: 100	
Roos *et al.*[46]	15/60 (25)	MASP-1: 100	C3: 60 C4d: 100	All were IgA2-negative Of 15 MBL-positive: C1q, 0%; ficolin-2, 100%; MASP-3, 100% Of 45 MBL-negative: C3, 82%; all others, 0%
(2 cohorts)	6/25 (24)	MASP-2: 100	–	All 19 MBL-negative also MASP-2–negative
Liu *et al.*[49]	45/131 (34)	–	–	MBL-positive: significantly higher SCr, urinary protein excretion, and ratio of hypertension; and significantly lower eGFR, serum albumin, and remission rate

eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; SCr, serum creatinine.
[a]The denominator for other components is the total number of patients with MBL-positive biopsies.

Table 3 | Associations between mesangial deposition of C4d and clinical outcomes in IgAN

Study	Associations observed in patients with IgAN and C4d mesangial deposition
Espinosa *et al.*[62]	C4d deposition in 39% of patients with IgAN; kidney survival at 20 years: 28% in C4d-positive patients and 85% in C4d-negative patients
Faria *et al.*[63]	C4d deposition in 55% of patients with progressive kidney disease (eGFR decline ≥50% or kidney failure) and 27% of patients with nonprogressive kidney disease during a mean follow-up of 4.7 years
Heybeli *et al.*[64]	C4d deposition (43% of patients) significantly associated with endocapillary hypercellularity, interstitial fibrosis/tubular atrophy, and mesangial IgM deposition
Nasri *et al.*[65]	C4d deposition (54% of glomeruli) significantly associated with serum creatinine, magnitude of proteinuria, the proportion of globally sclerotic glomeruli, and the proportion of tubulointerstitial fibrosis
Medjeral-Thomas *et al.*[32]	Compared with stable disease, patients with progressive disease (eGFR decline ≥50% or kidney failure, among other criteria) had an odds ratio of 8.3 for C4d deposition (at least mild C4d staining for 28% and 76% of patients with stable or progressive disease, respectively)
Segarra *et al.*[66]	C4d deposition (20% with IgAN and normal kidney function) independently predicted long-term kidney survival
Chua *et al.*[67]	Significantly poorer kidney survival in patients with C4d and microangiopathic lesions than in patients without these findings
Jiang *et al.*[68]	C4d deposition (34% of patients) independently associated with more than 3-fold risk of progressive kidney disease and more than 4-fold risk of kidney failure
Yang *et al.*[69]	Risk of disease progression (eGFR decline >20% or kidney failure) significantly greater in patients with vs. without C4d deposition (77% vs. 9%) during a median follow-up of 45 months; in a multivariate analysis, C4d deposition associated with a hazard ratio of 1.8 for disease progression

eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy.

pathway activation. Urinary levels of MBL and C4d have been shown to increase linearly with the proportion of glomerular crescents, which are prognostic of more rapid disease progression and poorer outcomes in IgAN.[71]

The role of serum MBL as a potential biomarker for disease severity in patients with IgAN is also presently uncertain and may be context-dependent. Some reports have shown that patients with IgAN do not have elevated serum MBL compared with healthy subjects.[48] Others have shown that serum MBL is not increased in the subset of patients with IgAN and MBL deposition in the glomerulus compared with patients without MBL deposition.[46] In an observational cohort study of 749 patients with IgAN and 489 healthy controls in China, a U-shaped association was observed between MBL levels and kidney outcomes.[72] Patients with IgAN and serum MBL deficiency (<100 ng/ml) had more than a 5-fold increase in the risk of poor kidney outcomes compared with patients with serum MBL levels between 100 and 3540 ng/ml. Individuals with very high MBL levels (>3540 ng/ml) in this study had more severe proteinuria, but the association with IgAN progression was not statistically significant after adjustment. Possibly, individuals with MBL deficiency who are prone to recurrent infections exhibit higher IgA levels making them susceptible to IgAN development and progression. Conversely, persistently high MBL levels might reflect activation of the acute-phase response, contributing to disease progression. Another level of complexity is added by the observation that circulating MBL levels and mesangial MBL deposits in patients with IgAN do not always correlate.[46] Thus, clinical interventional studies offer the best opportunity to shed light into the role of MBL in IgAN; the important question of whether there are situations where systemic inhibition of MBL is not beneficial currently remains unsolved.

The lectin pathway and thrombotic microangiopathy in IgAN

Concomitant thrombotic microangiopathy (TMA) in patients with IgAN is associated with worse outcomes and is an independent predictor of progression to chronic kidney disease and kidney failure.[73] The incidence of TMA in patients with IgAN has been reported to vary widely across different studies, from 2% to 53%.[74] Some cases are associated with severe hypertension, but cases have been reported in normotensive individuals with IgAN.[67,75,76] The incidence of comorbid microangiopathy and IgAN may vary by geography and ethnicity; higher incidences have been reported in South America,[73] Europe,[67,75,76] and China,[77] whereas lower incidences have been reported in Iran[78] and the United States.[79,80] The incidence of TMA in patients with IgAN may also be affected by the definitions and methods used to identify TMA. In the study with the highest reported incidence, 53% of patients with IgAN had TMA on kidney biopsy but only 6% of patients had laboratory evidence of TMA.[75] In another study, 20% of patients with IgAN had evidence of acute microangiopathy (fibrin, endothelial swelling or denudation, mesangiolysis, or microaneurysms in glomeruli; thrombi, endothelial swelling or denudation, intramural fibrin or intimal swelling in the arterioles; thrombi or myxoid intimal swelling in the arteries) or chronic microangiopathy (fibrous intimal thickening with concentric lamination and/or recanalization in the arterioles or arteries, with or without double contours in glomerular peripheral capillary walls), but only 1% had clinical TMA.[67] Thus, the concurrence of IgAN and clinical TMA may be infrequent.

Regardless of the incidence, TMA lesions in IgAN do appear to be associated with activation of the lectin pathway of complement. Arteriolar or glomerular deposition of C4d (in the absence of C1q) is associated with increased mean arterial pressure, arterial intima fibrosis, vascular lesions, and

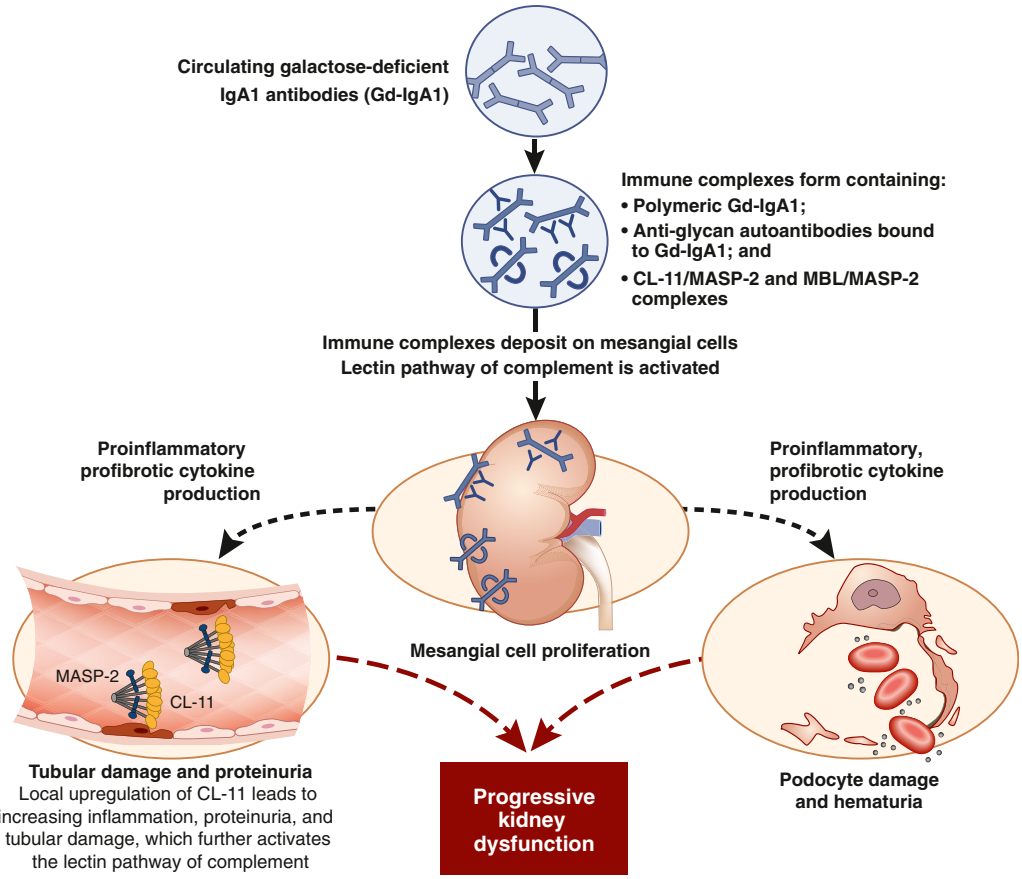

Figure 3 | Activation of the lectin pathway contributes to both tubular and podocyte damage in immunoglobulin A nephropathy. CL-11, collectin-11; Gd-IgA1, galactose-deficient IgA1; MASP-2, mannan-binding lectin-associated serine protease-2; MBL, mannan-binding lectin. Adapted with permission, from Barratt J, Lafayette R. MASP-2 inhibition as a potential strategy for the management of IgA nephropathy. Drugs Future. 2020;45:389–396.[88] https://doi.org/10.1358/dof.2020.45.6.3115216

chronic microangiopathy in patients with IgAN.[81,82] Patients with the triad of IgAN, microangiopathy, and C4d deposition have particularly poor kidney survival.[67] In one study in China, nearly half of the patients with microangiopathic lesions also had rare variants in complement-related genes, including pathogenic variants in 37% (alternative pathway, 28%; lectin pathway, 14%), further indicating that complement activation may be involved in the development of microangiopathic lesions in IgAN.[82] As described above, MASP-2 not only cleaves C2 and C4 but also activates the coagulation cascade. MASP-2 cleaves Factor XII to the active form, Factor XIIa, which initiates the coagulation cascade through the intrinsic pathway.[83] MASP-2 also activates the cleavage of prothrombin to thrombin.[28] Collectively, these effects promote fibrinogen turnover and clot formation to increase coagulation,[84,85] further contributing to TMA lesions in patients with IgAN.

Clinical evidence to support specific treatment in patients with both IgAN and TMA is lacking. In one case report, a patient with concurrent IgAN and microangiopathy (presenting as atypical hemolytic uremic syndrome) had persistent kidney failure despite treatment with steroids, plasma exchange, and C5 inhibition (eculizumab).[86] In a separate case report, a patient with concurrent IgAN and atypical hemolytic uremic syndrome responded to 5 months of C5 inhibition.[87]

The lectin pathway and tubulointerstitial fibrosis

The lectin pathway may contribute to tubulointerstitial fibrosis, and collectin-11/MASP-2 complexes are key mediators of this process (Figure 3).[88] Evidence supporting this hypothesis is primarily from animal models for kidney ischemia and protein overload. The pattern-recognition molecule collectin-11 binds to L-fucose on the surface of damaged cells in animal models of endothelial injury in the kidney, activating MASP-2 and leading to inflammation, fibrosis, and tubular damage.[52–54] After hypoxic stress in a kidney reperfusion injury model in mice, collectin-11 increases rapidly on the surface of tubular epithelial cells.[52] In ischemic kidney tissue, collectin-11 and its putative ligand, L-fucose, are aligned along the basolateral border of corticomedullary tubules.[52] Mice with *Colec11*$^{-/-}$ genetic mutations do not produce collectin-11; they have reduced deposition of C3d in tubules, less infiltration of inflammatory cells, less

severe histologic lesions, lower levels of extracellular matrix proteins in the tubular interstitium, and reduced tubule necrosis compared with wild-type mice after ischemia-reperfusion injury.[54] *In vitro*, collectin-11 promotes leukocyte migration and stimulates kidney fibroblast proliferation.[54] Local production of collectin-11 in the kidney in response to injury, rather than systemic production, appears to be important for the development of tubular fibrosis,[54] and this process is likely to also be relevant in IgAN.

The role of MASP-2 in tubulointerstitial fibrosis is further supported by data in the protein overload model. MASP-2–deficient (*MASP-2*$^{-/-}$) mice display reduced cell vacuolation, dilatation, protein casts, macrophage infiltration, cellular apoptosis, and inflammation- and fibrosis-related proteins in proximal tubules compared with wild-type mice.[89] The administration of a rodent-specific anti–MASP-2 antibody in wild-type mice subjected to protein overload reduces most of these tubular changes.[89]

In humans, collectin-11 is expressed throughout the body (thyroid and adrenal glands, lymph nodes, spleen, cardiac muscle, liver, gallbladder, pancreas, gastrointestinal system, kidney, bladder, reproductive organs, and adipose); in the kidney, it has higher expression than other pattern-recognition molecules.[23] IgA1 immune complexes from patients with IgAN increase expression of collectin-11 by mesangial cells, and the interaction between collectin-11 and IgA1 complexes on cell surfaces is thought to initiate activation of the lectin pathway and deposition of C3.[51] These results suggest that local production of collectin-11 in the kidney in response to injury, rather than systemic production, could contribute to the development of both glomerular and tubulointerstitial fibrosis, and that the inhibition of MASP-2 may be protective to both the glomeruli and tubulointerstitium in IgAN.

Current treatment of IgAN

Clinical practice guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) recommend preventing disease progression and minimizing the harmful side effects of immunosuppression as major treatment goals in IgAN and other glomerular diseases.[3] Multifaceted, optimized, supportive care includes rigorous control of blood pressure, dietary sodium restriction, and lifestyle modification to reduce cardiovascular risk. Inhibition of the renin-angiotension system with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to reduce proteinuria is first-line therapy in IgAN, regardless of whether the patient also has hypertension. If proteinuria persists above 0.75 g/d despite maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment for at least 90 to 180 days, then the patient should be offered the opportunity to take part in a clinical trial. Alternatively, a 6-month course of immunosuppression with a systemic glucocorticoid may be considered, but evidence supporting its likely risks and benefits should be discussed with patients, in particular those with an estimated glomerular filtration rate below 50 ml/min per 1.73 m^2.[3] Systemic glucocorticoids should be used with "extreme caution" or avoided in patients with risk factors increasing the likelihood of steroid-related toxicity. An enteric-coated, delayed-release formulation of budesonide has received accelerated approval in the United States and conditional authorization in the European Union to reduce proteinuria in adults with high-risk IgAN,[90,91] based on evidence that it reduced urine protein-to-creatinine ratio after 9 months of treatment compared with placebo.[92] At 2 years of follow-up, budesonide showed a statistically significant effect on estimated glomerular filtration rate loss versus placebo.[93] Non-corticosteroid immunosuppressive drugs do not have evidence to support their use in IgAN, except mycophenolate mofetil in Chinese patients.[94]

Recognizing the unmet medical need for treatments that target the underlying pathophysiology of IgAN, the KDIGO guidelines recommend participation in a clinical trial as preferable to a course of immunosuppression.[3] Supportive care may also include commencement of a sodium-glucose cotransporter-2 (SGLT2) inhibitor.[95–97] Another option to augment supportive care in IgAN is the addition of an endothelin A receptor antagonist. Sparsentan has received accelerated Food and Drug Administration approval to reduce proteinuria in adults with primary IgAN,[98] based on evidence that 36 weeks of sparsentan treatment significantly reduced proteinuria compared with irbesartan.[99] A placebo-controlled phase 3 trial of atrasentan (NCT04573478) in IgAN is ongoing.

Targeting the alternative and lectin pathways in IgAN

As previously discussed, the alternative pathway is generally active in IgAN and a number of investigational approaches to target this pathway have reached late-stage clinical trials. The Factor B inhibitor iptacopan was well tolerated, strongly inhibited activity of the alternative pathway, and reduced proteinuria through 6 months in a phase 2 study (NCT03373461)[100]; a phase 3 study is ongoing (NCT04578834). The Factor B inhibitor IONIS-FB-LRx also had an acceptable safety profile and reduced alternative pathway activity and proteinuria in a phase 2 study (NCT04014335).[101] Factor D inhibition with ALXN2050 is being investigated in a phase 2 study, but results are not yet available (NCT05097989). A phase 2 study of the Factor D inhibitor BCX9930 for the treatment of IgAN and other forms of nephropathy was recently terminated (NCT05162066). Other possible investigational approaches to target the alternative pathway, such as MASP-3 inhibition, are in earlier stages of clinical development.

As discussed above, lectin pathway activation is not seen in all cases of IgAN, but it is associated with more severe disease progression. There are several possible targets where the lectin pathway might be inhibited, including pattern-recognition molecules such as MBL and collectin-11, complement components such as C2 or C4, or MASP-2. Inhibiting pattern-recognition molecules in IgAN would require blocking both

MBL and collectin-11 to prevent both glomerular and tubulointerstitial injury, respectively. While inhibiting C2 or C4 would interfere with the pathophysiologic changes in IgAN through the lectin pathway, it would also negatively impact on normal classical pathway–mediated immune responses, including clearance of circulating immune complexes and response to microbial pathogens. This hypothesis is supported by evidence that the combined genetic deficiency of C2 and C4 is a strong risk factor for autoimmune conditions such as systemic lupus erythematosus.[102]

Given the role of MASP-2 activation of the lectin pathway in the pathophysiology of IgAN, the MASP-2 inhibitor, narsoplimab, is being assessed as a possible treatment for IgAN. A phase 2 clinical trial examined the safety and efficacy of narsoplimab treatment in adults with severe IgAN (NCT02682407). In the primary analysis, intravenous administration of narsoplimab once-weekly for 12 weeks was well tolerated, with no drug-related serious adverse events and no evidence of increased susceptibility to infections.[103] Additional 12-week courses of narsoplimab as needed for elevated urine protein excretion were also well tolerated, with a 38% decrease from baseline in urine protein excretion through 3 years of treatment and follow-up.[104] The overall annual rate of decline in estimated glomerular filtration rate was markedly slower in narsoplimab-treated patients (5.2 ± 2.1 ml/min/yr) than in a matched external comparator group of patients from the Leicester Renal Unit IgA Nephropathy Registry (8.6 ± 3.7 ml/min/yr).

Enrollment in a global, randomized, placebo-controlled phase 3 clinical trial of narsoplimab (ARTEMIS-IGAN; NCT03608033) is underway, with a final randomization target of 450 patients (225 per treatment arm) and first expected outcome data in 2023. Given the evidence, as discussed above, for greater comorbidity and worse outcomes among patients with concurrent IgAN and TMA, the ability to target both inflammation and coagulation via MASP-2 inhibition has therapeutic potential. Although narsoplimab has not been investigated for TMA in patients with IgAN, it has been studied in patients with COVID-19[105,106] and in patients with TMA. In a pivotal clinical trial of hematopoietic stem-cell transplantation–associated TMA, 17 of 28 (61%) patients responded to narsoplimab treatment.[107]

It remains to be determined if clinical outcomes associated with inhibition of the lectin pathway differ from those associated with other targeted therapies in development for IgAN, including inhibitors of the alternative pathway, inhibitors of the terminal complement pathway (i.e., C3, C5, and C5a receptor), or inhibitors of earlier hits in IgAN pathogenesis. Multiple studies are targeting these pathways and data will emerge. Further research is needed to answer important questions about the role of the lectin pathway in IgAN, including whether the pattern of complement activation changes over the natural history of the disease and what complement- or lectin pathway-specific biomarkers (in blood or urine) might be used to monitor the progression of IgAN in the kidney or responses to IgAN treatment. It also remains to be determined whether these biomarkers could be used to stratify patients with IgAN in clinical trials or to identify patients with IgAN in clinical practice who are more likely to benefit from a treatment that inhibits the lectin pathway.

Conclusions

Emerging evidence supports the role of the lectin pathway not only in the activation of complement in patients with IgAN but also as a potential mediator of fibrosis and disease severity. In particular, expression of the pattern-recognition molecule collectin-11 increases in response to IgA immune complex–activated mesangial cells, which appears to be a key step in triggering activation of the lectin pathway and tubular damage. Another pattern-recognition molecule for the lectin pathway, MBL, is also present in mesangial IgA deposits, and its association with disease severity is more complex. Available treatment options for IgAN have known limitations; treatment is generally supportive, and immunosuppression yields inconsistent benefits and carries significant safety concerns. Inhibiting MASP-2, the effector enzyme of the lectin pathway of complement, has the potential to target a key step in both local inflammation and fibrosis responsible for kidney injury. In a phase 2 clinical trial, the MASP-2 inhibitor narsoplimab was associated with clinically meaningful improvement and was well tolerated. A global, placebo-controlled phase 3 trial of narsoplimab for IgAN is underway. Although the focus of this review is on the lectin pathway in IgAN, other complement inhibitors (particularly inhibitors of the alternative pathway) are also being investigated in this rapidly evolving field of targeted therapy for IgAN and are in various stages of development.[108] For a chronic condition such as IgAN, as-needed cycles of treatment with a complement inhibitor or a longer-acting complement inhibitor may be required to achieve prolonged remission. The relative—and potentially additive or synergistic—benefits and risks of inhibiting different pathways of complement during long-term management of IgAN remain to be determined.

DISCLOSURE

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