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Is complement the main accomplice in IgA nephropathy? From initial observations to potential complement-targeted therapies

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ABSTRACT

IgA Nephropathy (IgAN) is the main cause of primary glomerulonephritis, globally. This disease is associated with a wide range of clinical presentations, variable prognosis and a spectrum of histological findings. More than fifty years after its first description, this heterogeneity continues to complicate efforts to understand the pathogenesis. Nevertheless, involvement of the complement system in IgAN was identified early on. Dysfunction of the immunoglobulin A (IgA) system, the principal offender in this disease, including modification of isoforms and glycoforms of IgA1, the nature of immune complexes and autoantibodies to galactose deficient IgA1 might all be responsible for complement activation in IgAN. However, the specific mechanisms engaging complement are still under examination. Research in this domain should allow for identification of patients that may benefit from complement-targeted therapy, in the foreseeable future.

1. Introduction to the complement system

The complement system is an important actor in innate immunity and a potent bridge between innate and adaptive immunity. Complement is found in the circulation in a biologically inactive state and can be activated by three arms: the classical (CP), lectin (LP), and alternative pathways (AP) (Dembic, 2021). Once activated, each pathway converges on C3 cleavage to the anaphylatoxin C3a and activated fragment C3b. This process can rapidly amplify, if not regulated, leading to terminal pathway activation characterized by the release of C5a and formation of the membrane attack complex (MAC – C5b9) (Chen et al., 2010). The CP is triggered by the interaction of the C1 complex with antibody-antigen complexes containing IgG or IgM. The LP is activated when mannan-binding lectin or other pattern recognition proteins such as ficolins (ficolin-1, ficolin-2 and ficolin-3) and collectins bind on carbohydrate residues present on surfaces such as bacterial cell membranes. These proteins are then complexed with MBL-associated serine proteases MASP-1, MASP-2 or MASP-3 (Ekdahl et al., 2018). The AP is permanently active at low levels in physiological states and accounts for 80% of complement system activity (Merle et al., 2015). Indeed, blockade of the AP by neutralizing factor D antibody in an in vitro assay involving CP activation inhibits up to 80% of C5b9 formation (Harboe et al., 2004). This result highlights the potent activity of AP regarding amplification of complement activation. Spontaneous and continuous hydrolysis of C3 is called the tick-over process, inducing conformational changes in C3. These structural modifications allow the binding of Factors B (FB) and D (FD) to the bioactive form of C3, C3(H2O), generating the fluid phase C3 convertase and thereby intensifying complement activation (Merle et al., 2015). Properdin stabilizes this C3 convertase. Tight regulation of this pathway is therefore mandatory for homeostasis. It is mainly regulated by complement Factor H (CFH), which degrades C3 to an inactivated form iC3b, in collaboration with Factor I (FI). Moreover, CFH action can be attenuated by complement FH-related (CFHR) proteins, which are highly homologous to FH but, importantly, lack the N-terminal complement regulatory region that is key to the inhibitory function of FH. Competition between CFH and CFHR shifts the balance between complement regulation and activation (Merle et al., 2015).

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2. Introduction to IgA nephropathy

IgA nephropathy (IgAN) is the main cause of primary glomerulonephritis worldwide and was described for the first time in 1968 by Berger et al. (Berger and Hinglais, 1968). The initial report described glomerular lesions, characterized by intercapillary deposits of IgA-IgG complexes associated with mesangial matrix expansion, in patients presenting with macroscopic or microscopic haematuria and mild-to-moderate proteinuria. IgAN leads to end-stage renal disease in approximately 30% of patients, with geographical differences in incidence and progression. Recurrence of IgA deposition in kidneys transplanted from healthy donors to IgAN patients implicates circulating factors involving IgA as the main culprit, rather than a primary issue arising from the kidney (Berger et al., 1984; van der Boog et al., 1999; Zagkotsis et al., 2018).

2.1. Introduction to the IgA system (Fig. 1)

IgA is the main mucosal immunoglobulin, and while it takes second place after IgG in the circulating compartment, IgA is produced more than any other immunoglobulin in the body when secreted forms are considered (van der Boog et al., 2005). Two subclasses of IgA are produced in humans: IgA1 and IgA2. These isotypes differ principally by the size of their hinge region. IgA1 has a uniquely extended hinge region enriched in serine and threonine residues on which O-glycans are linked (Ohyama et al., 2020). Glycosylation is one of the most important post-translational modification of IgA and tightly controls IgA effector function (Steffen et al., 2020). Besides O-glycans, IgA1 and IgA2 have 4 conserved N-glycan sites linked to asparagine motifs in the CH2 and CH3 domain of each of the 2 alpha heavy chains. Circulating IgA originates mainly from the bone marrow and consists of approximately 90% IgA1 and 10% IgA2, predominantly in monomeric forms (mIgA) over dimeric (dIgA) or polymeric forms (pIgA). Mucosal IgA exists mainly in dimeric/polymeric forms (Pabst, 2012). dIgA consists of two mIgA linked by the joining chain (J-chain) dIgA is transported into the gut lumen by the polymeric immunoglobulin receptor (pIgR), which binds dIgA at the basolateral side of epithelial cells and transports it to the apical membrane. During this transcytosis, dIgA becomes covalently linked to the pIgR and is released from the cell surface into the gut lumen via proteolytic cleavage, taking away a part of the receptor, the Secretory Component (SC), generating Secretory IgA (SIgA).

2.2. Alteration of IgA system in IgAN (Fig. 1)

In IgAN, IgA1 plasma concentration may be elevated (Peterman et al., 1991) with an increase in monomeric but also polymeric forms, linked to an increase in bone marrow IgA1 production and a decreased elimination rate by the liver. The first argument for altered IgA emerged from kidney eluates, revealing that IgA is mainly deposited as polymeric IgA1. Furthermore, the eluted IgA had a net negative charge, hinting towards abnormal glycosylation (Monteiro, 1985). Defects in the glycosylation status of circulating IgA1 (Mestecky et al., 1993; Lin et al., 2009; Suzuki et al., 2008) in IgAN is unanimously supported, with a decrease in galactosylation of the IgA1 hinge region. These peculiar glycoforms exhibit free N-Acetyl-D-Galactosamine residues and are found in the plasma compartment but also at mesangial level (Hiki et al., 1998, 2001; Amore et al., 2001; Moldoveanu et al., 2007). Galactose-deficient IgA1 (GdIgA1) are predisposed to self-aggregation and induce the generation of IgG directed against the modified hypogalactosylated hinge region, thereby giving rise to immune complexes (Tomana et al., 1999). Beside these O-glycans defects, differences in N-Glycan galactosylation, sialylation, bisection and fucosylation of circulating IgA have recently been found by mass spectrometry in IgAN patients (Dotz et al., 2021). Finally, SIgA has been found at low concentration in serum from IgAN patients and healthy donors after mucosal challenge (Eijgenraam et al., 2008) and has been detected in

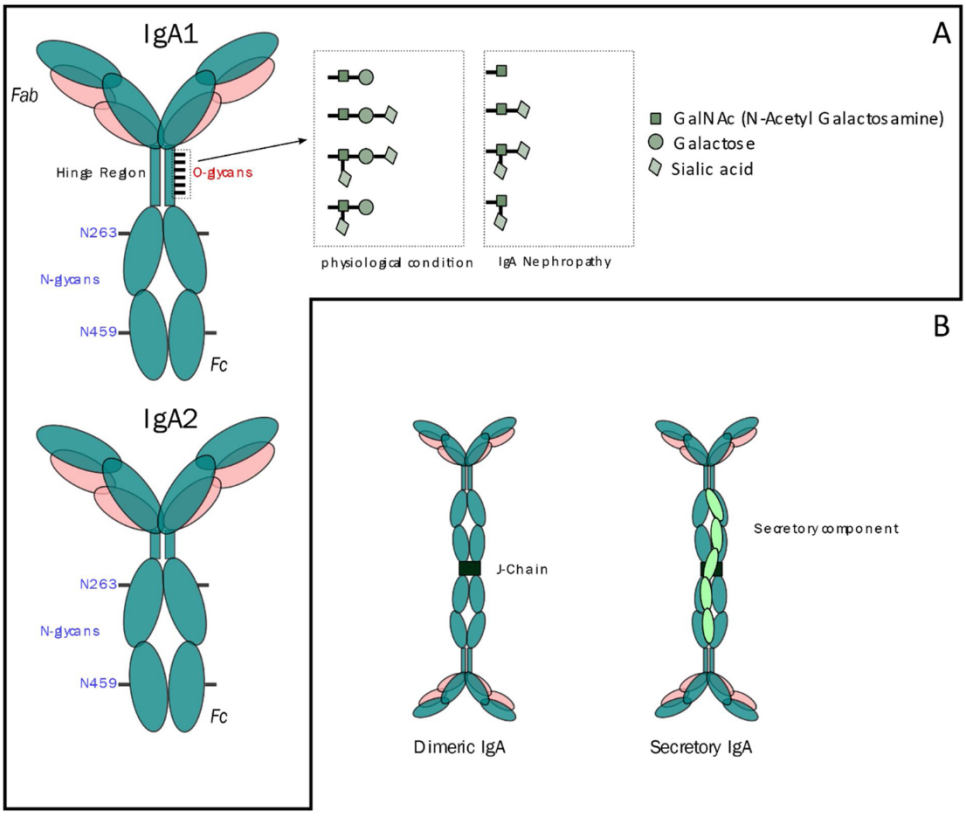

Fig. 1. Schematic diagram illustrating the structure of human IgA1 and IgA2, O-glycosylation pattern of IgA1 in physiological conditions and in IgA Nephropathy, N-glycosylation sites (**A**), dimeric and secretory IgA (**B**).

IgAN mesangium (Suzuki et al., 1990; Oortwijn et al., 2006; Eijgenraam et al., 2008).

IgAN pathogenesis follows a multi-hit process involving abnormal galactose deficient-IgA1 production, formation of IgA1-immune complexes (IgG anti-GdIgA1, IgA-CD89 s) (Launay et al., 2000; Berthelot, 2012) and deposition of the latter products on mesangial cells (Monteiro, 2018).

2.3. Role of immunoglobulins in complement activation

Immunoglobulins (Ig) can activate the CP (Daha et al., 2011). Binding of C1q occurs within the constant heavy domain of Ig and is especially effective in certain isotypes such as IgG1, IgG3 and IgM. In contrast, IgA lacks a site for C1q binding, explaining why it does not activate CP in vitro (Lucisano Valim and Lachmann, 1991). IgG, as IgA, are glycoproteins that can present variations in glycosylation of their N-glycans. Glycosylation, including fucosylation, of the Fc domain is mandatory for binding C1q. Agalactosyl glycoforms of IgG (Malhotra et al., 1995) can also bind MBL in vitro. These post-translational modifications, particularly engaged during inflammatory states, regulate IgG function (Zhou et al., 2021). The ability of IgA to activate complement pathways has long been controversial and the high diversity of its isoforms, glycoforms, associated antigens or differential nature of IgA-containing immune complexes may explain these discrepancies (Rifai et al., 1987).

Polyclonal monomeric IgA1 and IgA2 purified from healthy donors are equally able to induce complement AP activation, illustrating that O-glycans of the hinge region are not crucial for this process (Hiemstra et al., 1988). However, the effect of altered IgA N-glycosylation on AP activation would be an interesting path to explore. Modification of the N-glycosylation of IgG using N-Glycosidase F (PGNase F) is associated with reduced AP activation although, the mechanism is not clear. (Banda et al., 2008)

SIgA purified from colostrum interacts and activates serum complement to the same degree as monomeric IgA1 and IgA2 (Hiemstra et al., 1988; Boackle et al., 1974). In 1987, Hiemstra et al. demonstrated that chemically aggregated IgA activate complement AP in vitro with heterogeneous results depending on the size of the IgA aggregates and the method of aggregation (Hiemstra et al., 1987).

Polymeric IgA1 and IgA2 and denatured IgA1 (Terai et al., 2006), but not monomeric IgA, also bind the complement activating lectin MBL in vitro in a calcium-dependent manner (Oortwijn et al., 2006; Roos et al., 2001; Russell et al., 1989). MBL exclusively attaches to GlcNAc, mannose and fucose (Haurum et al., 1993) and since O-linked GalNAc is not a privileged ligand for MBL, it has been suggested that the binding could occur through the interaction with the N-linked glycans of the alpha heavy chain (Malhotra et al., 1995). A recent study by Medrano et al. confirmed mesangial co-deposition of C4d with specific IgA1 glycoforms in IgAN, and revealed N-Acetyl-D-Glucosamine and mannose residues as potential MBL ligands on IgA1 (Medrano et al., 2020). Interestingly, the secretory component (SC) on native SIgA masks these MBL binding sites (Royle et al., 2003) and conformational changes of its structure after bacterial binding or modification of environmental pH (Eijgenraam et al., 2008) could expose the GlcNAc residues and induce LP activation. These data corroborate the observation of strong mesangial co-localization of SIgA, MBL and C4d in IgAN (Oortwijn et al., 2006).

3. Clinical findings in IgAN in relation to complement system (Fig. 2)

In their original publication, Berger et al. described mesangial IgA deposits associated with less intense β1-C globulin deposits (Berger and Hinglais, 1968), a term that has since been replaced by complement C3. This was later confirmed by other studies demonstrating that nearly 75% of biopsies from IgAN patients were positive for C3 (McCoy et al., 1974) and C5b9 (MAC membrane attack complex of complement) (Miyamoto et al., 1988). These deposits have even been associated with haematuria during the disease course (Emancipator et al., 1987). Meanwhile, little was known about plasma complement activation until the late 1980′s (Wyatt et al., 1987). Initial studies demonstrated that C3 plasma levels were within normal range or slightly increased (Julian et al., 1983). It is important to note that C3 levels in White patients with progressive IgAN, in contrast to Chinese and Japanese patients, can be normal (Coppo, 2017). In vivo, there is a continuous physiological turnover of C3, and its level is influenced by various factors. Indeed, during an inflammatory state, C3 plasma concentration is often elevated, and a minor, but clinically relevant degree of complement activation may be underdiagnosed if there is no simultaneous measurement of activation and degradation products (Kirschfink, 2021). Wyatt et al., demonstrated that C3 activation - defined by high levels of plasma iC3b-C3d neoantigen assessed by radioimmunoassay - was observed in 37% of paediatric and 57% of adult European American IgAN patients, with variations during the disease course (Wyatt et al., 1987). Since these reports, many investigations have been carried out to determine which complement pathway is involved.

3.1. Classical pathway

IgAN is a disease involving immune complexes containing IgG which, in theory, should initiate the CP. The first investigators of complement in IgAN (Jennette and Hipp, 1985; Jennette, 1988; Rauterberg et al., 1987) found that C1q deposition was either absent or limited in glomeruli, when compared to diseases with clear CP involvement, such as lupus nephritis. This was confirmed in a cohort of 137 Japanese patients with only 6% of kidney biopsies showing C1q deposition (Boackle et al., 1974). Very recently, Tan et al. have reported C1q deposition in nearly 14% of Chinese IgAN patients and found that it was an independent risk factor for renal survival. Still, this result needs to be confirmed in multi-ancestry cohorts (Tan et al., 2021). It remains unclear however why the frequent IgG deposits in the mesangium, observed in nearly 40% of patients, including IgG autoantibodies against GdIgA1 are not associated more systematically with C1q deposits (Rizk et al., 2019). One explanation could be weak stability of C1q deposits in the mesangium (Berger, 2021). Currently, involvement of CP in IgAN pathogenesis cannot be completely ruled out.

3.2. Alternative pathway

This is, historically, the principal pathway implicated in IgAN pathogenesis. Increased plasma concentrations of “activated”C3″ including C3b, iC3b and C3dg is found in 30% of IgAN patients (Zwirner et al., 1997) and associates with proteinuria, haematuria and subsequent kidney function deterioration. Further analysis showed that the only measurement of plasma C3a does not have the same predictive values, emphasizing the need to measure the degradation products of complement factors in IgAN (Janssen et al., 2000). Because assessment of C3 degradation products is not a routine clinical measure worldwide, other prognostic factors have been evaluated, as the serum IgA/C3 ratio: a higher ratio is associated with poorer kidney outcome in adult and paediatric populations (Komatsu et al., 2004; Mizerska-Wasiak et al., 2015; Kawasaki et al., 2018). Glomerular staining of the breakdown products, notably C3c and C3d, is detected in almost all patients (Nakagawa et al., 2000; Bene and Faure, 1987). C3c deposition, a marker of recent complement activity, is associated with more severe haematuria and reduced glomerular filtration rate (Nakagawa et al., 2000). The deposition of properdin in 73% (Bene and Faure, 1987), factor H in 69–85% of kidney biopsies as well as Factor B (Bene and Faure, 1987; Miyazaki et al., 1984) make a strong argument for AP implication in IgAN. A recent study showed a positive correlation between Factor Ba plasma concentration and circulating GdIgA1 level, proteinuria and a negative correlation with estimated glomerular

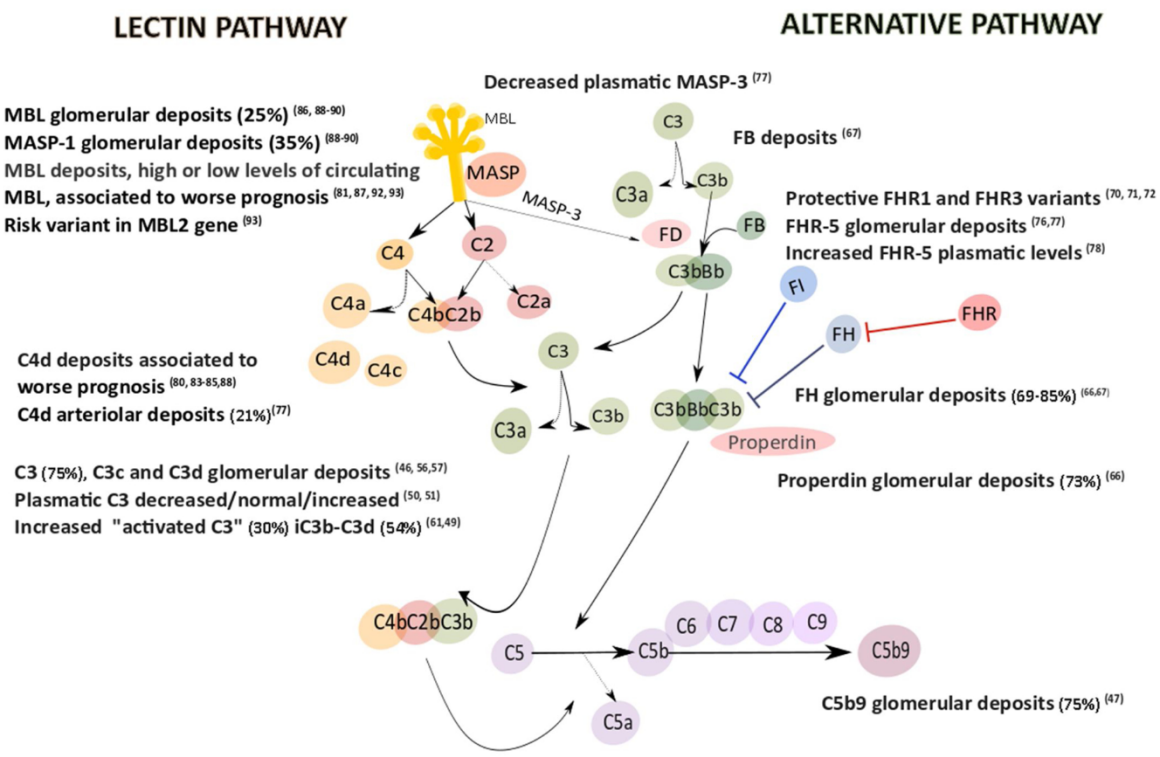

Fig. 2. Lectin and alternative complement pathway involvement in IgAN pathogenesis.
MBL (Mannose-Binding-Lectin), MASP (MBL-Associated Serine Protease), FH (Factor H), FHR (Factor H Related protein), FB (Factor B)

fraction rate (eGFR) (Chiu et al., 2021). However, Factor Ba can be increased in plasma from chronic kidney disease patients regardless of the nature of causal disease (Jalal et al., 2018) and further studies with GFR-matched controls is necessary.

In 2011, Gharavi et al. (Gharavi et al., 2011) performed a genome wide association study in Chinese and European cohorts of patients and identified a protective CFHR1 and CFHR3 loss of function-variant. CFHR1 and 3 are competitive antagonist of CFH that interfere with its regulation of C3b (Jullien et al., 2018a). This deletion of CFHR1 and CFHR3 protects against development of IgAN by increasing the functional activity of FH (Gharavi et al., 2011). Variants in CFH, CFHR1 and CFHR3 are associated with circulating CFH levels and modulate complement activation in IgAN (Zhu et al., 2015). The allele frequency in the general population of this CFHR1/CHR3 deletion, determined by multiplex ligand dependent probe amplification, is lower in China and Japan compared to African populations and homozygous deletion has been observed in 4–7% of European population (V Holmes et al., 2013). In a French monocentric White IgAN cohort, this homozygous deletion has been detected by RT-qPCR in 4% of patients whereas heterozygous deletion is found in 30.5% of patients and is associated to a decrease in immune complexes deposition but not to IgAN progression (Jullien et al., 2018b). It is however difficult to draw comparisons between these last two studies including different populations and different methods for the detection of gene deletions.

Another CFHR has been connected to IgAN pathogenesis: CFHR-5, detected by immunostaining in kidneys from patients (Murphy et al., 2002). It positively correlates with glomerular C3b/iC3b/C3c and C3dg deposition whereas FH staining is decreased in progressive IgAN disease, indicating a possible dysregulation of the AP in IgAN (Medjeral-Thomas et al., 2018). Finally, circulating levels of CFHR-5 are significantly elevated in IgAN compared to healthy donors and is an independent risk factor for disease progression (Zhu et al., 2018). However, there is uncertainty whether these observations are disease-specific or rather the reflection of chronic kidney disease.

3.3. MBL (mannose-binding lectin)/MASP (MBL-associated serine protease) pathway

While the literature already provided convincing and tangible results about AP activation in IgAN, involvement of LP, discovered in the early 1990's, emerged less than ten years later. Indeed, detection of mesangial C4 and C3 deposits in the absence of C1q, is highly suggestive for LP implication in IgAN. However, this point should be tempered by the fact that C1q does not bind covalently to its ligands, in contrast to C4b, explaining its potential higher mesangial clearance rate (Berger, 2021). Differentiating CP and LP involvement in IgAN could therefore be assessed by the measurement of C1q-C4 or C3 complexes, as already published (Wouters et al., 2005). Compellingly, in multiple studies, presence of mesangial C4 degradation products, notably C4d, as well as MBL is associated with a more severe disease, and worse prognosis in both adult (Espinosa et al., 2009; Liu et al., 2013; Espinosa et al., 2014; Faria et al., 2015) and paediatric IgAN (Fabiano et al., 2017). Mesangial C4d is found in 20–38% of IgAN patients (Espinosa et al., 2009, 2014; Segarra et al., 2018), MBL deposits in 25%–35% (Roos et al., 2001; Liu et al., 2013; Endo et al., 1998; Roos et al., 2006) and MASP-1 in 80% of IgAN vasculitis kidney biopsies (Endo et al., 2000). These observations are more frequent in patients exhibiting IgA1 and IgA2 mesangial deposition, suggesting a particular role of IgA2 in LP activation (Hisano et al., 2001, 2005).Recently, Faria et al. (Faria et al., 2015) identified arteriolar C4d deposits in 21% of IgAN patients and its association with arterial intimal fibrosis, chronic microangiopathy and correlation with mean arterial pressure, likely explaining the specific vascular involvement in some IgAN patients (Cai et al., 2019). MBL level is correlated to histopathological parameters and may be a non-invasive biomarker for predicting the prognosis of IgAN (Liu et al., 2012). A risk variant in *MBL2* (MBL gene) is associated with reduced circulating MBL levels and an increased risk for ESRD in IgAN, in a Chinese cohort (Ouyang et al., 2019). Other indicators of poor prognosis have been identified, including high serum levels of MBL (Faria et al., 2015; Guo et al., 2017) which is contradictory to previous results and not fully understood yet,

and low-levels of circulating MASP-3 (Medjeral-Thomas et al., 2018). Intriguingly, MASP-3 inhibits the binding of MASP-2 with MBL, historically known as a negative complement regulator, but has been recently implicated as the exclusive pro-factor D activator. This major result illustrates the dual role of MASP-3 and a fundamental link between AP and LP, which should be further studied in IgAN (Dobó et al., 2016).

3.4. Systemic and/or local activation?

Whether complement activation occurs systemically or *in situ* in IgAN is of importance to the current understanding of pathogenesis and treatment guidance. The main site of C3 synthesis is the liver, but extrahepatic synthesis has been described (Laufer et al., 2001). In particular, studies have shown its expression in glomerular epithelial cells (Sacks et al., 1993a), and in primary mesangial cell cultures (van den Dobbelsteen et al., 1994) under IL-1β and IL-6 stimulation. Other complement factors can be expressed by mesangial cells, such as Factor H (van den Dobbelsteen et al., 1994) and C4 (Sacks et al., 1993b) under the control of cytokines and growth factors.

Besides cytokines, and in particular IL-6 which plays a role in IgAN pathogenesis, the main question is to assess the possibility of local complement activation by immune complexes containing IgA. Answers to these considerations have been provided by Schmitt et al., who demonstrated that stimulation of mesangial cells with galactose-deficient polymeric IgA1 induces C3 secretion (Schmitt et al., 2014) and mesangial proliferation. Indeed, this hyperplasia could be partly complement-driven. In fact, mesangial cells physiologically express C3a and C5a receptors: their inhibition represses mesangial cell proliferation, Il-6 and MCP-1 expression and reduces kidney damage in a mouse model of IgAN (Zhang et al., 2017). Furthermore, C5aR mRNA overexpression has been described in mesangial cells from IgAN patients (Abe et al., 1998). Finally, in IgAN, renal cortical complement C3 gene expression is detected in more than half of the patients and is significatively more frequent in patients exhibiting severe IgAN lesions (Montinaro et al., 1997). These observations shed light on local complement involvement in IgAN development. Restricted mesangial complement activation would theoretically enhance cell lysis because of terminal complement deposition however, this feature is not observed in IgAN. In vitro experiments showed that upon complement activation induced by immune complexes, mesangial cells have increased Decay-Accelerating Factor (DAF) membrane expression and synthesis (Shibata et al., 1991; Cosio et al., 1994). DAF (CD55) is a membrane protein present on most cell types, protecting them from complement induced cell lysis by inhibiting formation and accelerating the degradation of C3 and C5 convertase. These general observations have been confirmed in IgAN kidneys, where glomerular and interstitial DAF and C3 mRNA expression correlate with the degree of corresponding glomerular and tubulo-interstitial injuries (Abe et al., 1998). In summary, it is likely that both circulating and locally produced complement factors contribute to mesangial inflammation, triggered by the deposition of IgA1 immune complexes.

3.5. Is complement activation associated with specific clinico-histological features of IgAN?

IgAN is a very heterogeneous disease, and some patients exhibit a systemic form with digestive, rheumatologic and skin involvement called IgA vasculitis (IgAV). There are still conflicting results about the differential prognosis between IgAN and IgAV with nephritis (Pillebout, 2021). If populations are matched for age, histology and treatment factors, renal prognosis is equal in IgAN and IgAV (Oh et al., 2012). A Japanese study concerning 10 IgAV patients with nephritis, compared to 19 age-matched IgAN patients, demonstrated that serum levels of C3, C4, C4BP, Factor H and Factor I were not different between these two populations. However, no histological comparison nor any follow-up were carried out (Endo et al., 2000). Currently, no data in favour of a higher level of complement activation in IgAV compared to IgAN is published, but larger-scale studies are necessary. However, low levels of circulating C3 is an independent risk factor for kidney involvement (Chan et al., 2016) and IgA/C3 ratio could be a predictive tool for steroid resistance in paediatric IgAV patients (Shin et al., 2005).

Extracapillary proliferation is associated with poor kidney outcome especially in patients with crescents involving >25% of glomeruli (score C2)(Trimarchi et al., 2017). Presence of crescents seems to be more frequent in Chinese and Japanese cohorts, concerning 48.3% and 61% of IgAN biopsies compared to 15.3% in White patients (Barbour et al., 2019). In a monocentric Japanese study, patients exhibiting extracapillary proliferation had higher immunofluorescence score for C5b-9, MASP1/2/3, properdin and factor B, whereas serum C3 and C4 levels were comparable (Itami et al., 2020). However, kidney outcome was similar in this study, regardless of the C score: differential steroid use might explain this observation.

Microangiopathy with or without thrombosis is frequently encountered in IgAN biopsies, with active and/or chronic features in up to 50% of IgAN patients (El Karoui et al., 2012). Glomerular C4d staining is more prevalent in biopsies with microangiopathy lesions and is associated with poorer renal survival after correction for blood pressure and eGFR (Chua et al., 2019). Association of this histopathological characteristic with abnormalities of complement regulation such as CFHR1, CFHR3 deletion and FH autoantibodies still needs to be addressed in large-scale studies.

In conclusion, very limited data are available regarding associations between complement activation, complement pathways and clinico-histological features of IgAN. Both serological and renal evaluation of complement activation in IgAN will be needed to assess which subgroup of IgAN patients would be candidates for complement blockade therapy.

4. Experimental models of IgAN and involvement of complement (Table 1)

IgAN develops following a complex, multi-hit process, which explains why it has been a struggle to obtain a representative experimental animal model of the disease for over 50 years. Difficulties encountered in establishing IgAN experimental models arise from interspecies differences in structure and function of IgA and its main receptor, the FcαR (CD89). While humans display two IgA subtypes, mice and rats have only one IgA which differs from human IgA1 by displaying a shorter hinge region without O-glycosylation. Moreover, rodents circulating IgA is mainly in dimeric form, contrary to humans (Grey et al., 1970). Finally, mice do not express CD89 IgA receptor but rats do express a CD89 homologue (Monteiro and Van De Winkel, 2003; Maruoka et al., 2004).

4.1. Spontaneous mouse models

The ddY mouse strain exhibits spontaneous IgAN, characterized by the development of glomerulonephritis with proteinuria associated with IgA, IgG, IgM and C3 mesangial deposits. However, the age of onset and severity is very heterogeneous, due to genetic variation induced by historical outbred stock management. A genome-wide association study identified four candidate loci linked with the early onset of the disease in ddY mice. Intercrossing of early-onset ddY mice for more than 20 generations induced the generation of the grouped-ddY mouse model featuring high-proteinuria, kidney failure at 24 weeks of age and IgA with C3 mesangial co-deposits (Okazaki et al., 2012). Finally, within the initial ddY strain, some mice exhibit high serum levels of IgA, but interbreeding those ddY strains (HIGA mouse model) does not worsen kidney involvement. Additional analysis demonstrated stronger staining for complement C3, C5b-9, C1q, C4, MBL, MASP2, factor B and properdin in the grouped-ddY strain compared to HIGA mice, highlighting the implication of the 3 pathways in this model (Hashimoto et al., 2012).

Table 1
Complement involvement in experimental models of IgAN.

	Rodent strain or model	Year of publication	Complement factors deposits in glomeruli	Ref.
Spontaneous	ddY strain (mice)	1986	C3	(118)
	HIGA (mice)	1997	C3, C5b9, C1q, C4, MBL, MASP2, Factor B, Properdin	(118, 119)
	Grouped-ddY (mice)	2012	C3, C5b9, C1q, C4, MBL, MASP2, Factor B, Properdin	(118)
Transgenic	CD89 transgenic (mice)	2000	Not published	(28)
	α1KICD89Tg (mice)	2012	C3	(29, 121)
	Uteroglobin antisense transgenic (mice)	2000	C3	(122,123)
	Human Bcl-2-transgenic (mice)	2004	Not published	(130)
	Human BAFF-transgenic (mice)	2006	Not published	(131)
	B1,4-galactosyltransferase-I-KO (mice)	2007	C3	(133)
	CD37 deficient (mice)	2018	Not published	(132)
Induced	Anti DNP IgA immunization (mice)	1979	C3	(35, 134)
	Anti DNP monomeric or polymeric IgA immunization (rat)	1983	C3 - No C4 nor C1q.	(135, 136)
	Gliadin immunization (mice)	1989	Not published	(138)
	Vomitoxin-exposed (mice)	1989	No C3 deposition	(141)
	Sendai Virus immunization (mice)	2001	C3	(142)
	Streptococcus mutans induced periondontal disease (rat)	2020	C3	(143)
	Artificial IgA Fc polymers immunization (rat)	2021	C3	(137)
	NALT stimulation of ddY mice with TLR9 ligands	2021	C3	(144)

HIGA : High Immunogloublin A.
Bcl-2 : B cell lymphoma 2.
BAFF : B cell activating factor.
DNP : dinitrophenyl.

4.2. Transgenic and humanized mouse models

As CD89 is not expressed in mice, its overexpression by conventional transgenesis in C57BL/6 or BALB/c strain (CD89Tg mice) results in the development of haematuria and mild proteinuria associated with mesangial hyperplasia and mouse IgA deposits but only in old animals (at 40 weeks of age) (28). Mice express only one type of IgA, different from human IgA1. Previous studies have shown that mouse IgA or mouse immune complexes containing IgA lack the capacity to activate complement compared to human IgA (Pfaffenbach et al., 1982). For this reason, a humanized mouse model has been established with knock-in human IgA1 at the murine IgM switch locus as well as being CD89 transgenic: α1KICD89Tg mice. These mice develop haematuria, albuminuria and altered renal function at 12 weeks of age and exhibit serum immune complexes containing human IgA1. Furthermore, histological examination shows predominant mesangial IgA1 with C3 co-deposition, glomerular macrophage infiltration and mesangial cell proliferation. In contrast, mice expressing IgA1 alone do not have kidney function alteration and failed to display mesangial complement deposition (Oruc et al., 2016). Whether soluble CD89, a highly glycosylated protein, could contribute to explain complement deposition in the α1KICD89Tg mice remains to be demonstrated. Other transgenic models have been developed, such as the uteroglobin antisense-transgenic mice. Uteroglobin is an anti-inflammatory protein secreted by mucosal epithelia, with high-affinity for fibronectin, interfering with IgA-fibronectin spontaneous interaction. This model is characterized by microhaematuria, albuminuria and glomerular IgA, C3 and collagen deposits (Zheng et al., 1999; Zhang et al., 2000). However, uteroglobin does not seem to be implicated in IgAN pathogenesis in humans (Coppo et al., 2002).

More recently, a particular interest in the role of B-cells in IgAN led to the generation of two transgenic models: human Bcl-2 (B-cell lymphoma 2) and BAFF (B-cell activating factor). Bcl-2 is usually overexpressed in B cells in autoimmune states, inducing a defect in the regulation of B-cell apoptosis and enhancing the systemic IgA immune response (Marquina et al., 2004a). B-cell activating factor (BAFF) is also a protein of interest in IgAN, involved in antibody class-switching and B cell survival. Overexpression of human BAFF has been described in IgAN (Cao et al., 2020; Zheng et al., 2015, 2017; Sallustio et al., 2021). Both models exhibit high levels of hypogalactosylated IgA and IgA mesangial deposition, though no data is available concerning complement activation (Marquina et al., 2004b; McCarthy et al., 2011). CD37, another key molecule in B cell function, has been shown to be decreased in B cells from IgAN patients (Rops et al., 2018). CD37 deficiency in a rodent model leads to glomerulonephritis with dominant IgA deposition and mesangial cell proliferation. In contrast, double knock out mouse for CD37 and IL6 do not display any sign of glomerulonephritis, suggesting that CD37 may inhibit the IL-6 pathway and thereby protect against IgAN (Rops et al., 2018)

Finally, galactosylation status of IgA is essential in the pathophysiological process of IgAN. Murine IgA has N-glycans but not O-glycans, contrary to human IgA1. Recently, Nishie et al. proposed a new murine model deficient for β-1,4-galactosyltransferase (β4GalT-I), the enzyme responsible for transferring galactose to the terminal N-acetylglucosamine of IgA in mice, resulting in high serum IgA levels with increased polymeric forms, albuminuria, haematuria, mesangial matrix expansion, glomerulosclerosis, mesangial IgA and mesangio-parietal C3 deposits (Nishie et al., 2007).

4.3. Induced models

The first murine model published by Rifai et al. is an IgA immune complex glomerulonephritis induced by anti DNP (dinitrophenyl) IgA in BALB/c mice. Mice exhibit haematuria, mild mesangial proliferation, and mesangial IgA deposits, even after complement depletion by cobra venom factor. Although complement is not necessary for the development of the disease in this model, C3 mesangial deposits are observed in non-complement depleted mice (Rifai et al., 1987). Moreover, immunization with immune complexes combining DNP, anti DNP IgA and IgG containing complement-fixing sites induces hematuria and glomerular C3 deposits in BALB-c mice. This is not observed with IgG lacking the ability to fix complement, implying the possible role of complement in haematuria (Emancipator et al., 1987; Sevillano et al., 2017). This experimental procedure was optimized a few years later in a rat model challenged with DNP-F(ab'2) anti Thy1 followed by systemic administration of monomeric or polymeric IgA anti-DNP. Rats immunized with polymeric IgA, in contrast to monomeric IgA, demonstrate acute proteinuria, mesangial IgA and C3 deposition. No deposits of C1q nor C4 are observed, suggesting the implication of the alternative pathway (Stad et al., 1993). Complement depletion in those rats did not prevent the IgA mesangial deposits but abolished the glomerular inflammation (Stad et al., 1994).

Recently, a new approach has been proposed, involving administration of biotinylated recombinant Fc region of IgA capable of

polymerisation in the presence of streptavidin. Systemic administration with these artificial IgA Fc polymers induces very rapid and transient IgA and C3 mesangial deposition (Xie et al., 2021).

IgAN is closely related to mucosal immunity, and flares of the disease are commonly observed after mucosal stimulation by antigens or infectious mucosal-associated diseases. Exposure to food antigens such as gluten and ovalbumin may contribute to the pathogenesis of IgAN. Interestingly, gliadin, a component of gluten, induces mesangial IgA deposits in BALB-C mice (Coppo et al., 1989). Moreover, we previously reported that a gluten-free diet in α1KICD89Tg mice is associated with a decrease in mesangial IgA1 deposits and a significant decline in C3 glomerular staining (Papista, 2015). Further studies revealed the ability of gliadin, exhibiting lectin function, to bind IgA1 (Coppo et al., 1992) and sCD89 (Papista, 2015). Exposure to vomitoxin, a fungal contaminant of cereals, induces an increase in serum IgA levels in a rodent model, as well as IgA mesangial deposition (Pestka et al., 1989), though no complement co-deposits have been observed.

Oro-pharyngeal mucosal challenge may also be interesting in experimental models of IgAN. Inoculation of Sendai virus in mice leads to hyperactivation of Th2 cells and induction of microhaematuria, glomerular IgA and less intense C3 deposits in BALB/c mice (Chintalacharuvu et al., 2001). More recently, rat models of periodontal disease and dental caries induced by specific strains of streptococcus, such as *Streptococcus mutans*, have been developed. These rats develop an IgA-like glomerulonephritis, characterized by IgA and C3 mesangial deposition (Naka et al., 2021). The role of the environment in IgAN pathogenesis is essential. Early onset-ddY mice housed in germ-free conditions do not develop IgAN. Notwithstanding, nasal-associated lymphoid tissue (NALT) stimulation of these mice by TLR9 ligands reconstitutes IgAN, characterized by IgA and C3 mesangial co-deposits (Kano et al., 2021).

Renal deposition of complement factors has been observed in most of these rodent models, but none have been used to publish a complement inhibition strategy. Evaluating which complement pathways is involved in each model according to serum and histological parameters would be interesting, as the impact of this activation on phenotype and kidney prognosis. Drug induced inhibition of the LP and AP seems the more practical way to test our hypothesis rather than inducing IgAN in complement deficient mice. Currently, there is an increased race towards the generation of therapeutic humanized monoclonal antibodies: efficacy assessment of such drugs in experimental IgAN models is limited by the need for mice expressing humanized complement proteins. Interestingly, an humanized C3 mouse model has been recently developed (Devalaraja-Narashimha et al., 2021). Modification of therapeutic humanized antibodies to improve inhibition in rodents is also possible, as already described (Orsini et al., 2016). Some drugs as LNP023 (Schubart et al., 2019) and RNAi ALN−CC5 (Kusner et al., 2019) are fully compatible for complement inhibition in mice and humans and would be good candidates for investigating complement role in this disease. Novel studies assessing complement blockade in these rodent strains are eagerly expected.

5. Discussion and treatment options (Fig. 3)

Despite significant research in IgAN pathogenesis since 1968, there is still no immunosuppressive treatment specific for IgAN. Currently, in "classical IgAN" (*ie* non-rapidly progressive IgA glomerulonephritis), the first line of treatment consists of 6-months supportive treatment including renin-angiotensin-aldosterone system blockade and second line use of corticosteroids when there is persistent proteinuria > 1 g/day (KDIGO, 2021). Delay in finding specific drugs can be explained by the heterogeneous clinical and histological presentation of IgAN, ranging from asymptomatic IgA mesangial deposition to rapidly progressive glomerulonephritis, with an evolution towards end-stage renal disease in approximatively 30% of cases. When considering treatment options, a clear estimation of individualised patient's risk of disease progression is therefore mandatory. Proteinuria and GFR are the only prognostic biomarkers used currently (KDIGO, 2021). Results of the VALIGA study showed that there was a variability in outcome that was not explained by either histological MEST-C score, nor by clinico-biological parameters (proteinuria, GFR, blood pressure), indicating that other prognostic elements are to be found. Of note, circulating GdIgA1 is not considered as a prognostic marker, due to conflicting published results (Suzuki et al., 2014; Wada et al., 2018; Camilla et al., 2011). The IgAN Prediction Tool has been recently proposed (Barbour et al., 2019), and its use recommended for prognostication of primary IgAN. This score includes already-known risk factors of bad prognosis such as reduced GFR, hypertension, protein excretion above 1 g/day at diagnosis, and the histological MEST-C score (M1, S1, T1/2). However, this tool cannot be used for immunosuppressive treatment decisions (KDIGO, 2021).

An important factor is therefore whether the magnitude of complement activation by AP or LP might be another prognostic element that could improve the risk prediction models and be a tangible biomarker on which a specific treatment could be proposed. Presently, answers to this major question cannot be drawn.

Large-scale observational international prospective studies with thorough follow-up analysis of new markers, such as IgA/C3 ratios, circulating C3 degradation products, CFHR levels, IgA isoforms, glycoforms and immune complexes, genetic variants of CFH-CFHR genes, and initial in situ kidney complement deposition pattern of the LP and AP pathways, in addition to the markers already validated, will improve our knowledge and address the place of complement blocking therapies in IgAN.

So far, complement inhibition in IgAN has only been tested as salvage therapy. Use of Eculizumab, a selective C5 inhibitor, has been reported in a few published cases of IgAN or IgAN vasculitis patients with extracapillary proliferation and acute kidney failure (Rosenblad et al., 2014; Ring et al., 2015). Despite initial improvement in kidney function, it did not prevent end stage renal disease developing in both cases. This treatment also failed in a patient with relapsing rapidly progressive IgA nephropathy shortly after kidney transplantation (Herzog et al., 2017). Timing of treatment was sporadic and duration of therapy was short in these case reports.

A significant number of new drugs targeting AP, LP or common pathways have been developed recently. Indeed, complement inhibitors targeting the AP are now under investigations in IgAN, using Iptacopan (LNP023), a selective factor B inhibitor (NCT04578834). Complement blocking therapies targeting common factors of the 3 pathways are also under evaluation: Ravulizumab, a long-acting C5 inhibitor engineered from Eculizumab (NCT04564339), Cemdisiran (ALN−CC5), a GalNAc-conjugated RNAi, inhibiting liver production of C5 (NCT03841448), and APL-2, a C3 inhibitor peptide (NCT03453619) are being assessed in phase 2 trials. C5a receptor antagonist, as Avacopan, could also be a valuable drug in IgAN (Bruchfeld et al., 2017) and has proven its efficacy in other complement-mediated diseases such as ANCA vasculitis (Jayne et al., 2021). Recently, the safety of Narsoplimab (OMS721), a fully human monoclonal antibody inhibiting Mannan-binding lectin-associated serine proteinase 2 (MASP-2) has been confirmed in a phase 2 trial including IgAN patients (Lafayette et al., 2020), and a phase 3 trial is ongoing (NCT03308033).

These trials currently enrol patients with GFR $\geq$ 30 mL/min and urine protein:creatinine ratio > 1 g/g, regardless of complement activation parameters. We hope that analysis of such elements and outcomes will allow identification of which IgAN patients will benefit from these therapies.

Interestingly, other promising molecules specifically inhibiting LP pathways, like small heparin and heparan-sulfate derived oligosaccharides have been recently discovered (Talsma et al., 2020), paving the way to the future of complement-blockade therapy.

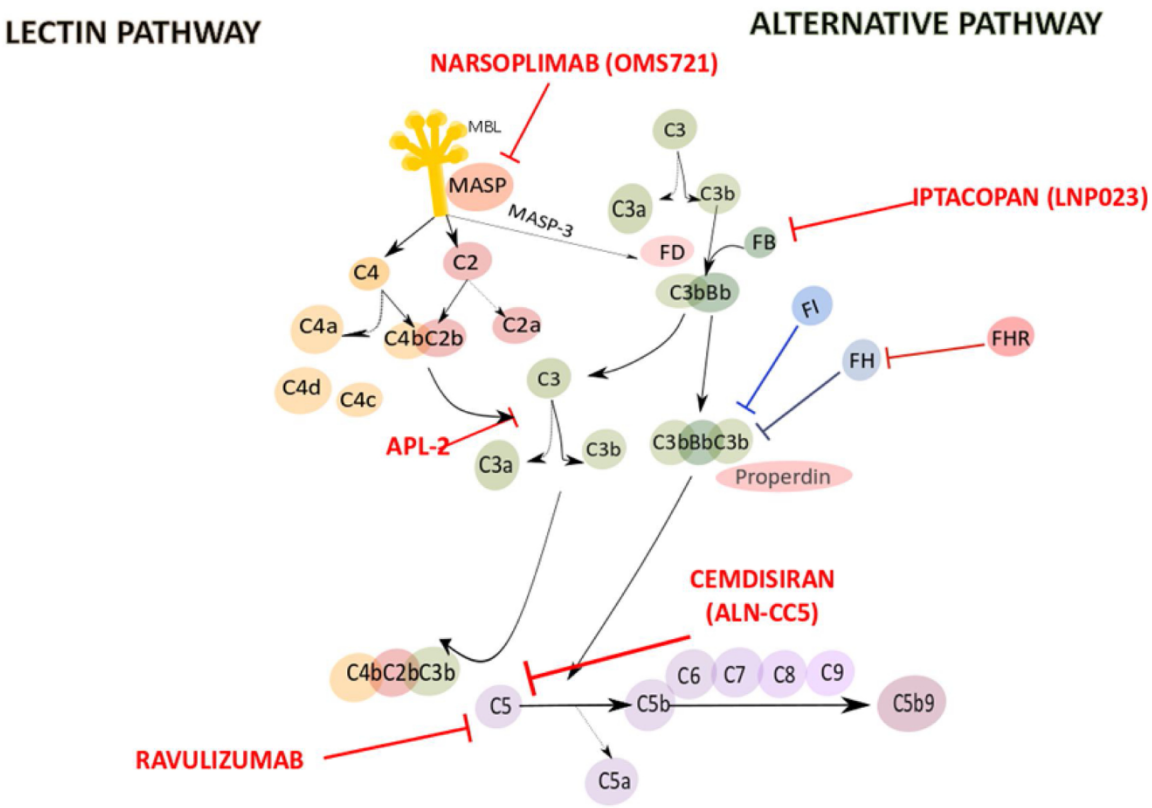

Fig. 3. Current Complement blocking therapies in phase II or III trials in IgAN.
MBL (Mannose-Binding-Lectin), MASP (MBL-Associated Serine Protease), FH (Factor H), FHR (Factor H Related protein), FB (Factor B)

6. Conclusion

This review summarizes the historic and current understanding of the implication of complement in IgAN pathophysiology. It highlights the potential contribution of IgA isoforms, glycoforms and immune-complexes to this process, both in systemic and renal compartments. Elucidating the mechanisms behind heterogenous LP and AP activation will open the way to a better understanding of disease pathogenesis and to individualised, complement-targeted treatment in IgAN.

Author statement

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Declaration of Competing Interest

The authors declare no conflict of interest.

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