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Review

The role of complement in IgA nephropathy

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ABSTRACT

IgA nephropathy (IgAN) is common and often progresses to end stage renal disease. IgAN encompasses a wide range of histology and clinical features. IgAN pathogenesis is incompletely understood; the current multi-hit hypothesis of IgAN pathogenesis does not explain the range of glomerular inflammation and renal injury associated with mesangial IgA deposition. Although associations between IgAN and glomerular and circulating markers of complement activation are established, the mechanism of complement activation and contribution to glomerular inflammation and injury are not defined. Recent identification of specific complement pathways and proteins in severe IgAN cases had advanced our understanding of complement in IgAN pathogenesis. In particular, a growing body of evidence implicates the complement factor H related proteins 1 and 5 and lectin pathway as pathogenic in a subset of patients with severe disease. These data suggest complement deregulation and activity may be dominant drivers of renal injury in IgAN. Thereby, markers of complement activation may identify IgAN patients likely to progress to significant renal impairment and complement inhibition may emerge as an effective method of preventing and reducing glomerular injury in IgAN.

1. Introduction

1.1. IgA nephropathy overview

IgA Nephropathy (IgAN) is the most common primary glomerulonephritis in the world. A diagnosis of IgAN is associated with an average reduction in life expectancy of 6–10 years (Hastings et al., 2018; Jarrick et al., 2019). Approximately 40% of IgAN patients older than 30 years age at diagnosis develop end stage renal disease (ESRD) over 20 years (D'Amico, 2004). However, IgAN is characterized by a broad range of clinical presentations and courses. This translates into different presentations in children and adults. Furthermore, clinical severity differs markedly with gender, ethnicity and race. It is estimated that in 5.8% of cases there may be a family history or genetic predisposition for the disease (Julian et al., 1985). Hence, it is thought that IgAN can encompass different biological processes, which presents the question of whether IgAN is a single pathogenic entity. Stratification of patients on clinical and histology features is currently difficult, which greatly complicates the therapeutic approach.

IgAN is an autoimmune disease characterized by abnormal IgA1 synthesis and glycosylation, resulting in imbalanced increase of circulating galactose deficient IgA1 (gd-IgA1). This anomalous IgA1 can form complexes with specific autoantibodies, forming gd-IgA1 immune complexes (gd-IgA1-IC). The gd-IgA1-IC deposit in glomeruli, a process that leads to mesangial cell proliferation and matrix expansion by mechanisms that are not completely understood (Heineke et al., 2017). Recurrence of this glomerular entity after renal transplantation suggests systemic immune dysregulation, rather than local renal abnormalities, is pathogenic in IgAN. Consistent with this, peripheral blood mononuclear cells are hyperactivated in IgAN, showing decreased regulation of the cellular machinery involved in antigenic processing (Floege, 2011; Wyatt and Julian, 2013).

The most consistent clinical finding in IgAN is the presence of hematuria; approximately half of patients present with outbreaks of macroscopic gross hematuria (MGH) and most other patients have microscopic hematuria. However, the pathogenesis and clinical significance of MGH are not understood. Bouts of macroscopic hematuria are more common in children and early stages of adult IgAN and are concomitant with mucosal infections, usually in the respiratory and, occasionally, gastrointestinal tracts (Haas et al., 2008). Interestingly,

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mesangial IgA deposition also coincides with these infections (Robert et al., 2015), indicating that dysregulation of the mucosal immune system and mucosa-kidney axis may be important in the pathogenesis of haematuria in IgAN (Suzuki et al., 2011a). In adult IgAN patients, MGH can precipitate acute renal failure and 25% of patients over 50 years age may not recover renal function if MGH is prolonged beyond 10 days (Gutierrez et al., 2007). Classically, recurrent episodes of macroscopic haematuria were considered an infrequent clinical manifestation after 40 years age. However, the degrees of haematuria and proteinuria in IgAN are wide-ranging. Furthermore, the demographic of IgAN patients seems to have changed; recent series have found a significant increase in the average age of IgAN patients and the proportion of patients over the age of 65 years at presentation (Gutierrez et al., 2018). Acute kidney injury, MGH and nephrotic range proteinuria are more common in patients older than 65 years, and the reasons for this are not known (Gutierrez et al., 2018).

Proteinuria, the presence or development of arterial hypertension and reduced glomerular filtration at diagnosis are the clinical factors that influence the development of chronic kidney disease (CKD).The amount of proteinuria is particular relevant in IgAN. Presenting proteinuria greater than 0.5 g/day is significantly associated with worse renal outcomes (Reich et al., 2007). Consequently, therapeutic approaches aim for proteinuria reduction. The use of renin-angiotensin-aldosterone system blockers is widely recognized as the best therapeutic approach in patients with IgAN and proteinuria greater than 0.5–1 g/day and arterial hypertension (Chapter 10, 2011).

IgA Nephropathy can manifest diversely, ranging from isolated microscopic hematuria to rapidly progressive glomerulonephritis. The natural history and clinical outcomes of IgAN are also diverse and include spontaneous remissions (5–15%, less common in adults) and rapidly progressive glomerulonephritis (< 10%), although slowly progressive CKD (30–40%) and "benign" evolution (40–50%) are the most common (Bartosik et al., 2001; Yoshikawa et al., 1990). Inherent variation in the rate of IgAN progression makes randomized controlled trials difficult to design and interpret. Therefore, risk scores are needed that predict and stratify patients to fast or indolent courses (Coppo, 2018).

About 7%–15% of IgAN patients present with malignant hypertension (Sevillano et al., 2015; El Karoui et al., 2012). IgAN with malignant hypertension is characterized by severe renal impairment at presentation and commonly progresses to ESRD. Renal biopsy demonstrates mild to moderate glomerular sclerosis and interstitial fibrosis in more than 80% of cases. Interestingly, renal biopsy also demonstrates thrombotic microangiopathy (TMA) in 30%–100% patients, although laboratory evidence of TMA, such as thrombocytopenia or schistocytes on blood film, is much less common (Sevillano et al., 2015; El Karoui et al., 2012). TMA is characteristic of microangiopathic syndromes in which complement dysregulation seems to play an important pathogenic role, including atypical haemolytic uraemic syndrome (aHUS) (Noris et al., 2012). IgAN patients with malignant hypertension and TMA demonstrate the potential for complement to drive glomerular injury in IgAN.

1.2. IgA nephropathy pathogenesis

IgAN is an autoimmune disease influenced by multiple genetic, ethnic and environmental factors. Although the protagonist seems to be gd-IgA1, multiple events contribute to IgAN and renal damage. The currently accepted model of pathogenicity in IgAN is the *"four-hit"* model (Fig. 1) (Suzuki et al., 2011b).

1.2.1. First hit: elevated serum gd-IgA1 levels

IgA is the most synthesized antibody in humans, abundant on mucosal surfaces and fundamental to mucosal antigen responses and host-commensal homeostasis. There are two IgA subclasses, IgA1 and IgA2. About 80% of serum IgA is IgA1 (Breedveld and van Egmond, 2019). The subclasses differ mainly by the structure of the heavy chain, specifically in the hinge region (HR). IgA1 contains numerous *O*-linked glycans and two *N*-linked glycosylation sites per heavy chain, whereas IgA2 does not possess *O*-glycans and contains two additional heavy chain *N*-glycan sites (Woof and Russell, 2011). Also, the IgA1 HR is 13 amino acids longer than IgA2. The structural differences make IgA1 susceptible to bacterial proteases. In contrast to other immunoglobulins, IgA is found in monomeric (mIgA1) and polymeric (pIgA1) forms. Monomeric IgA1 predominates in blood whereas pIgA1 is found mainly in external secretions (Woof and Mestecky, 2005). Most serum mIgA is produced in bone marrow; secretory pIgA is synthesized locally in mucosal tissues. Polymeric IgA1 composition is diverse and includes dimeric, secretory and immune complexes of IgA (Oortwijn et al., 2006).

IgAN patients show greater proportions of poorly O-galactosylated IgA1 in circulation compared to healthy individuals (Hiki et al., 2001; Coppo and Amore, 2004; Moldoveanu et al., 2007). These glycosylation defects seem to have a high component of heritability. The gd-IgA1 glycoforms are polymeric, and normally produced at mucosal surfaces as part of innate immune responses (Boyd et al., 2012). Therefore, abnormal innate immunity responses to mucosal infections or antigens may be involved in the gd-IgA1 production in IgAN. Supportive of this, a role for Toll-like receptors (TLR), which cause polyclonal lymphocyte proliferation (Meng et al., 2014; Nishikawa et al., 2000) and formation of circulating immune complexes (Robert et al., 2015; Barratt et al., 2007), may be involved in IgAN pathogenesis. Coppo R et al. demonstrated overexpression of TLR4 in circulating mononuclear cells from patients with IgAN (Coppo et al., 2010). Mucosal TLR9 activation induces B cell activation factor (BAFF) overexpression in dendritic cells, B cell expansion and increased IgA synthesis (Kajiyama et al., 2011) all of which may influence IgAN pathogenesis (Suzuki et al., 2011b). Recently, the potential anti-proteinuric benefit of hydroxychloroquine, an immunomodulator that inhibits TLR as well as the production of cytokines and chemokines, has been demonstrated in IgAN (Liu et al., 2019).

1.2.2. Second hit: anti-gd-IgA1 antibodies

Gd-IgA1 is the target for antiglycan autoantibodies (Maixnerova et al., 2019). The glycan-specific autoantibodies are often characterised by the replacement of serine with alanine in the complementarity-determining region 3 of the heavy chain variable region (Suzuki et al., 2009). This change increases the affinity of binding to O-linked glycans, particularly exposed N-acetylgalactosamine (GalNac), on gd-IgA1. This alteration arises from somatic mutation during active immune responses, perhaps following exposure to viruses or bacteria that express GalNac (Wyatt and Julian, 2013). Anti-gd-IgA1 IgG levels correlate with disease severity, specifically with the amount of proteinuria. Also, their presence in renal biopsies correlates with mesangial and endocapillary proliferation (Bellur et al., 2011).

1.2.3. Third hit. Increased circulating gd-IgA1- immune complexes (IC)

IgAN is characterised by mesangial deposition of IgA1 and complement proteins. The IgA1 deposits derive from pathogenic circulating IC and contain aberrantly glycosylated pIgA1, which shows galactose deficiency in HR O-linked glycans (Hiki et al., 2001; Allen et al., 2001; Mestecky et al., 2013). IgA complexed with soluble Fcα receptor (CD89) can be detected in serum from IgAN patients but not other diseases, and a mouse model of IgAN implicates soluble CD89-IgA complexes in disease pathogenesis (Launay et al., 2000). However, other studies have found soluble CD89-IgA1 complexes are neither specific nor relevant to IgAN development (van der Boog et al., 2003; Vuong et al., 2010). The mesangial cells represent the primary target of these pathogenic immune deposits and the unique anatomy of the mesangium, located between the fenestrated endothelium and the glomerular basement membrane, makes it a deposit focus. Gd-IgA1-IC deposition can be increased during episodes of macroscopic hematuria,

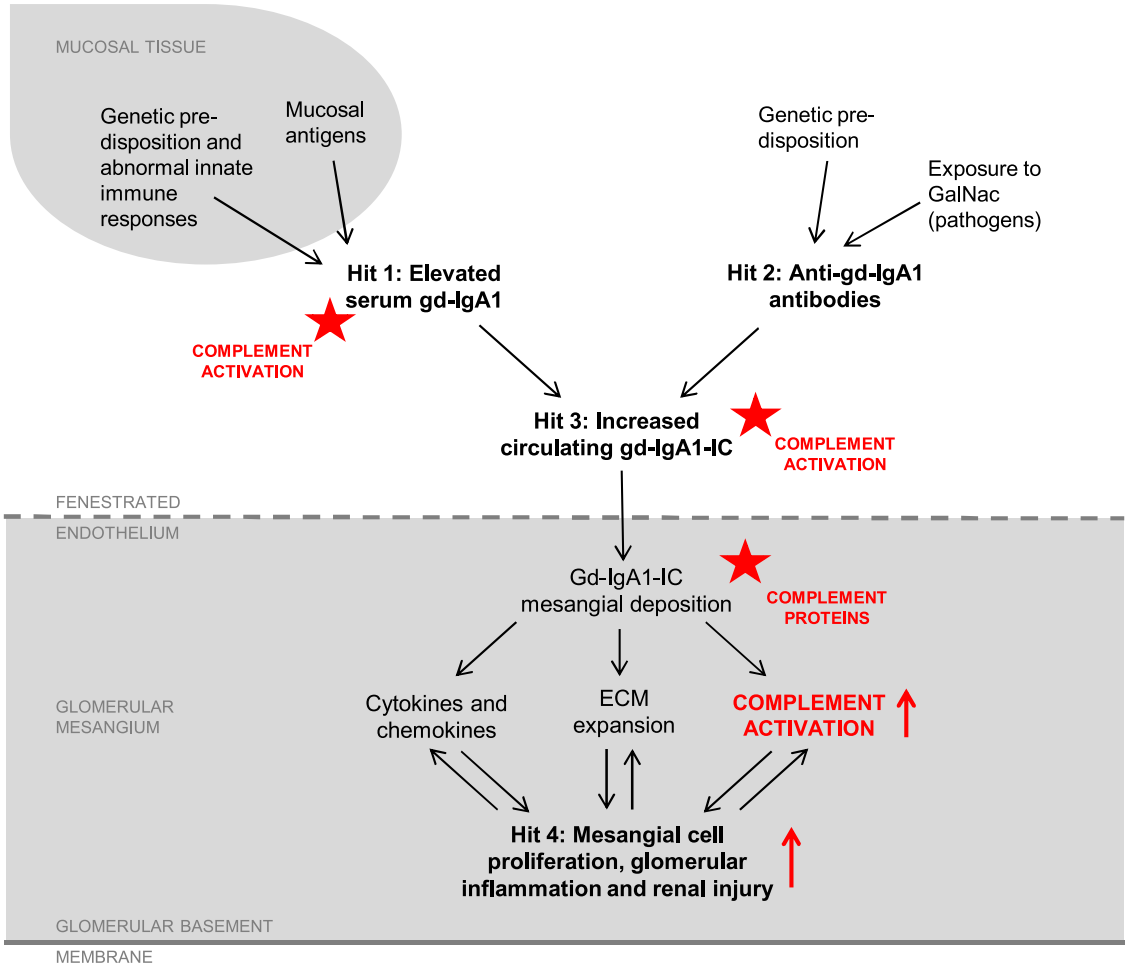

Fig. 1. Complement in the multi-hit pathogenesis of IgA nephropathy. IgA Nephropathy (IgAN) pathogenesis involves multiple hits (Wyatt and Julian, 2013; Yeo et al., 2018). Genetically predisposed individuals mount abnormal immune responses to common and environmental pathogens. This leads to Hit 1, elevated serum levels of galactose-deficient IgA1 (gd-IgA1), Hit 2, the overproduction of autoantibodies with heavy chain variable region characteristics that recognise gd-IgA1, and Hit 3, the formation of circulating immune complexes of gd-IgA1 and anti-gd-IgA1 autoantibodies (gd-IgA1-IC). Presumably by traversing glomerular fenestrated endothelium, gd-IgA1-IC deposit in mesangium and trigger cellular responses, cytokine release, complement activation, and extracellular matrix (ECM) expansion. The result is Hit 4; mesangial cell proliferation, glomerular inflammation and renal injury. The multi-hit theory does not currently explain why glomerular IgA1 and circulating gd-IgA1 and gd-IgA1-IC are detected in healthy individuals (Suzuki et al., 2003; Gale et al., 2017). Evidence of complement activation has been identified at multiple points in IgAN pathogenesis (indicated with red stars). For example, polymeric gd-IgA1 can trigger alternative and lectin pathway activation *in vitro*. Alternative pathway activation proteins have been identified in patient-derived circulating gd-IgA1-IC (Hiemstra et al., 1987; Roos et al., 2001). The ability for gd-IgA1-IC to induce mesangial cell responses *in vitro* is dependent on a heat-labile factor, which could be complement (Yanagihara et al., 2012). And immunohistology evidence of glomerular alternative, lectin and terminal pathway activation correlate with IgAN severity (Medjeral-Thomas et al., 2018; Roos et al., 2006). Due to its self-amplifying nature, complement activity at any step in IgAN pathogenesis would amplify (red arrows) glomerular complement activation, inflammation and renal injury. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

perhaps after binding receptors that recognize the pathogenic IC (Novak et al., 2005).

1.2.4. Fourth hit. Mesangial cell proliferation, glomerular inflammation and renal injury

This is characterized by extracellular matrix expansion, complement activation and cytokine release. Some cytokines can injure podocytes, alter podocyte gene expression and glomerular filtration and induce proteinuria (Lai et al., 2009; Trimarchi and Coppo, 2019). However, how gd-IgA1 interacts with and damages glomerular cells is not clear. Mesangial cells have IgA receptors and are candidates for IC clearance, initiation of injurious mechanisms, and localizing complement activation. The binding of pIgA1 to mesangial cells increases the production of IL-8 *in vitro* (Oortwijn et al., 2006). But direct binding of IgA-containing immune complexes to mesangial cells has been difficult to demonstrate. Mesangial cells from IgAN patients, but not healthy controls, overexpress the transferrin receptor (CD71), which binds pIgA1 and co-localizes with IgA1 immune deposits. However, its blockade does not completely prevent IgA binding to mesangial cells (Moura et al., 2014). Recently β-1,4 galactosyltransferase was identified as a potential receptor for the Fc portion of IgA (Molyneux et al., 2017). Tissue deposition of IgA1-IC can trigger local complement activation, although how this occurs is unclear. One challenge is to identify mechanisms that link glomerular IgA1 deposition with complement activation, inflammation and the spectrum of clinical features encompassed by IgAN.

recent data suggests IgAN could be a podocytopathy, which may force current pathogenesis models to be modified. Experimental assays indicate mesangial cell stress, as seen in IgAN, can influence podocyte behavior. Mesangial cells are fundamental to maintain glomerular stability. In IgAN, mesangial expansion can be accompanied by capillary prolapse that could cause podocyte detachment (Kriz, 2018; Bellur et al., 2017). This mesangium-podocyte cross-talk may explain the occurrence of proteinuria and tubulo-interstitial injury in IgAN; the release of cytokines such as TNF, IL-6 and Angiotensin II could induce

inflammation and subsequent glomerulosclerosis. Thereby, hematuria could be involved in mesangial expansion and podocyte damage through mechanisms including mesangial architecture modification.

Many components of IgAN pathogenesis have been described. However, we do not understand the spectrum of glomerular responses to deposited gd-IgA1 seen in IgAN. This ranges from apparent immunological tolerance and absent glomerular reaction to progressive CKD and ESRD. Consequently, we are unable to consistently identify patients who would benefit from immunosuppression, leading to a number of negative randomized clinical trials in IgAN (Lv et al., 2017). A growing body of evidence suggests the alternative, lectin and terminal complement pathways influence glomerular inflammatory and injurious responses to deposited IgA1 and contribute to IgAN disease severity.

2. Alternative pathway in IgAN

The earliest descriptions of IgAN by Jean Berger noted that C3 deposits often accompanied mesangial IgA (Berger, 1969). Mesangial co-deposition of C3 and IgA is characteristic of IgAN, being present in at least 90% of biopsies (Evans et al., 1973). The alternative pathway (AP) is the main complement cascade activator in IgAN and is principally responsible for C3 deposition. Mesangial C4, and particularly the activation fragment C4d is frequently identified in IgAN biopsies. This, together with the almost universal absence of C1q in IgAN deposits indicates that lectin pathway (LP) also activates complement in IgAN, and that the classical pathway (CP) is unlikely to contribute to pathogenesis (Rauterberg et al., 1987). In other words, the glomerular presence of C3 alone implies AP activity; the presence of C4 and C3 in the absence of C1q implies LP activity, possible with AP dependent amplification; and CP activity would be evidenced by glomerular C3, C4, C1q and IgG. A summary of the evidences supporting the association of AP and LP complement components in IgAN disease is depicted in Table 1.

Regarding the AP, multiple well-established associations (Bene and Faure, 1987; Wyatt et al., 1987) and recent evidence of factor H related protein (FHR)1 and FHR5 involvement indicate a role for the AP in IgAN pathogenesis.

2.1. Established associations

Typically, components of the AP found in the renal biopsies of IgAN patients include C3, in more than 90%, properdin in 75%–100% and factor H (FH) in 30%–90% of cases (Bene and Faure, 1987; Maillard et al., 2015; Zhang et al., 2009). Other AP regulators, such as the FHR proteins, have also been identified (Murphy et al., 2002; Paunas et al., 2017). C3 mesangial co-deposition with IgA1 correlates with the severity and progression of IgAN, suggesting activation of complement particularly *via* AP contributes to glomerular injury (Maillard et al., 2015; Kim et al., 2012). Glomerular C3 deposits may help differentiate IgAN from isolated lanthanic IgA deposits found in up to 4–16% of the population (Waldherr et al., 1989; Suzuki et al., 2003), which are especially common in East Asian populations (Li and Yu, 2018; Kiryluk et al., 2012).

Evidence of complement activation is not limited to kidneys. Decreased plasma C3 levels with increased C3 activation products (iC3b and C3d) were observed in some IgAN patients and indicate that systemic complement activation and subsequent regulation through the AP may also occur in the fluid phase (Wyatt et al., 1987; Kim et al., 2012; Zwirner et al., 1997). Supporting this, *in vitro* assays using plate-bound, or aggregates of, IgA showed IgA1 were able to trigger the complement cascade and C3 cleavage *via* the AP; and proteomic analyses of circulating gd-IgA1-IC revealed the presence of C3 breakdown products like iC3b, C3c, and C3dg (Hiemstra et al., 1987; Roos et al., 2001; Knoppova et al., 2016). This evidence of AP dependent complement activation and regulation on the essential effector molecule of IgAN suggests gd-IgA1-IC act as complement activating surfaces. Importantly, the ability of IgA-containing IC formed from cord blood gd-IgA1 and either anti-glycan IgG or patient-derived gd-IgA1-specific IgG to activate mesangial cells is dependent on a heat-sensitive serum factor, presumably complement (Yanagihara et al., 2012). The presence of IgA1 receptors such as CD71, which is overexpressed by mesangial cells in IgAN patients, makes the mesangium primary target for the pathogenic IC deposition (Moura et al., 2014).

C3 mesangial co-deposition, C3 consumption and increased plasma C3 fragments correlate with unfavorable IgAN histopathology features and outcomes, supporting the relevant contribution of AP to the pathogenesis of glomerular injury (Wyatt et al., 1987; Zwirner et al., 1997). In the following sections we aim to summarize key recent advances that further support the involvement of complement activation in IgAN pathogenesis, and shed light on different mechanisms of AP dysregulation.

2.2. delCFHR3-R1

Perhaps the most striking recent links between IgAN and complement system activity were the genome wide association studies that identified protective associations for IgAN within the *CFH* locus on chromosome 1q32. These large, replicated genetic studies implicated a role for the FHR proteins in IgAN pathogenesis. The protective allele identified tags the deletion polymorphism of the FHR1 and FHR3 genes (*delCFHR3-R1*) (Gharavi et al., 2011). This allele associates with protection from IgAN. The risk of developing IgAN is reduced by 26% by the presence of the allele in heterozygosity (odds ratio (OR) = 0.74) and by 45% in homozygosity (OR = 0.55). Histopathology studies showed that *delCFHR3-R1* was associated with reduced mesangial C3 deposition and tubulointerstitial injury in Chinese cohorts (Zhu et al., 2014; Yeo et al., 2018). *delCFHR3-R1* is the most common rearrangement among the FHR family, with a wide range of allelic frequencies in different populations: 0% to 5% in East Asians and Native Americans, 20% in Europeans, and up to 50% in African populations. Interestingly, allele frequencies correlate with IgAN epidemiology; the protective *delCFHR3-R1* allele is more prevalent in African populations where there is lower disease prevalence (Holmes et al., 2013; Yeo et al., 2019).

By interacting with the same ligands, such as C3b and glycosaminoglycans, members of the FHR family can modulate FH regulatory functions on surfaces. The *CFHR1–5* genes likely originated from the *CFH* gene by tandem duplication events. While all FHR proteins conserve homology with the ligand recognition sites of FH, they lack the regulatory region of FH (Jozsi et al., 2015). Thus, FHR proteins modulate FH function by competition with ligands and deregulate complement activation on cell surfaces. Conversely, the inappropriate function of FHR proteins may determine susceptibility to complement mediated injury. This mechanism may explain the protective association of *delCFHR3-R1* with IgAN; reduced or absent FHR1 and FHR3 increase the regulating capacity of FH, reducing AP activity and preventing the potential risks of complement activation. Interestingly,*delCFHR3-R1* is in strong linkage disequilibrium with a *CFH* haplotype that produces higher levels of plasma FH, (Zhu et al., 2014) further supporting the protective effect that *delCFHR3-R1* mediates in IgAN.

2.3. Circulating FH and FHR1 levels

Recent analyses of circulating FH and FHR1 levels highlight the importance of AP dysregulation to IgAN. Two independent studies showed FHR1 plasma levels were significantly higher in IgAN patients than controls irrespective of the *delCFHR3-R1* allele carriage (Medjeral-Thomas et al., 2017; Tortajada et al., 2017). The authors also observed a negative correlation between FHR1 levels and eGFR. Higher FHR1 associated with disease progression to CKD. Notably, while FH levels did not associate with disease status, the relative abundance of these

Table 1
Evidence of complement activity in IgA nephropathy (IgAN). Associations between complement variants and activation markers and IgA nephropathy risk and severity.

Complement Protein		Evidence in IgA Nephropathy	References
Lectin Pathway	C4d	Glomerular deposits associate with IgAN severity and worse renal outcomes.	(Roos et al., 2006; Espinosa et al., 2014)
	MBL	Glomerular deposits associate with IgAN severity.	(Roos et al., 2006; Endo et al., 1998)
		Low of high plasma levels associate with IgAN severity.	(Guo et al., 2017; Ouyang et al., 2019)
		Altered levels in urine.	(Roos et al., 2006; Shi et al., 2015)
	L-ficolin	Found in glomerular deposits.	(Roos et al., 2006)
		Increased plasma levels	(Medjeral-Thomas et al., 2018)
	M-ficolin	Increased plasma levels.	(Medjeral-Thomas et al., 2018)
	MASP-1	Found in glomerular deposits.	(Roos et al., 2006)
		Increased plasma levels.	(Medjeral-Thomas et al., 2018)
	MASP-2	Found in glomerular deposits.	(Roos et al., 2006)
	MASP-3	Found in glomerular deposits.	(Roos et al., 2006)
		Reduced plasma levels correlate with IgAN severity	(Medjeral-Thomas et al., 2018)
	Map19	Increased plasma levels correlate with IgAN severity	(Medjeral-Thomas et al., 2018)
Alternative Pathway	C3 and C3 activation fragments	C3 deposits correlate with IgAN severity and progression.	(Berger, 1969; Evans et al., 1973)
		Low C3 in plasma correlates with worse renal outcomes.	(Kim et al., 2012)
		Increase plasma of iC3b and C3d correlate with worse outcomes.	(Wyatt et al., 1987; Zwirner et al., 1997)
		iC3b, C3c, and C3dg observed in IgA1-IC complexes.	(Knoppova et al., 2016)
	Factor H	Found in glomerular deposits (30%-90%).	(Bene and Faure, 1987; Zhang et al., 2009)
		Partial deficiencies. Variants in 4 of 5 cases affect expression.	(Wyatt et al., 1991; Tortajada et al., 2017)
		Increase levels in urine correlate with worse renal damage.	(Zhang et al., 2009)
	FHR1	Found in glomerular deposits.	(Murphy et al., 2002; Paunas et al., 2017; Medjeral-Thomas et al., 2018)
		Absence confers protection (del*CFHR3-1*).	
		Elevated plasma levels correlated with IgAN progression	(Gharavi et al., 2011; Zhu et al., 2014) (Medjeral-Thomas et al., 2017; Tortajada et al., 2017)
	FHR3	Absence confers protection (del*CFHR3-1*).	(Gharavi et al., 2011)
	FHR5	Found in glomerular deposits	(Murphy et al., 2002; Paunas et al., 2017; Medjeral-Thomas et al., 2018)
		FHR-5 variants resulting in increased binding to C3b.	
		Elevated plasma levels correlated with worse renal outcome	(Zhai et al., 2016)
		Glomerular FHR5 deposition associate with IgAN progression	(Medjeral-Thomas et al., 2017; Zhu et al., 2018) (Medjeral-Thomas et al., 2018)
	Properdin	Found in glomerular deposits (30%-90%).	(Bene and Faure, 1987)
		Anecdotal cases with partial deficiency.	(Wyatt et al., 1991)
	Factor I	Anecdotal cases with partial deficiency.	(Maillard et al., 2015; Tortajada et al., 2017)
	C3a	Induce secretory phenotype in mesangial cells.	(Wan et al., 2007)
Terminal Pathway	C5b9 (MAC)	Found in glomerular deposits	(Rauterberg et al., 1987; Paunas et al., 2017)
		Correlation with severity of renal injury and tissue inflammation.	(Stangou et al., 2008; Qiu et al., 2014; Zhang et al., 2014)
	C5a	Mesangial activation and histological IgAN markers associated with C5aR activation.	(Zhang et al., 2017)

MBL, mannan-binding lectin; MASP, MBL associated protease; Map, MBL associated protein; FHR, factor H related protein; MAC, membrane attack complex.

two proteins varied with severity; elevated FHR1/FH ratio also associated with worst clinical features independent of the *delCFHR3-R1* allele carriage (Medjeral-Thomas et al., 2017; Tortajada et al., 2017). In addition, four FH variants associated with decreased plasma FH levels were identified in the Spanish cohort of 106 IgAN patients (Tortajada et al., 2017). Another case of partial deficiency of FH in association with IgAN has been described (Wyatt et al., 1991). The *delCFHR3-R1* is associated with higher circulating C3 and FH levels, lower plasma C3a levels and less mesangial C3 deposition (Zhu et al., 2014). Thereby, the protective effect of *delCFHR3-R1* is likely mediated by greater FH regulatory activity (Zhu et al., 2014), while unbalanced FHR1/FH ratio from elevated FHR1 or decreased FH plasma levels aggravate the disease by compromise FH regulatory activity causing AP dysregulation.

Circulating FHR1 levels may be related to renal function. In the non-complement-mediated autosomal dominant polycystic kidney disease (ADPKD), higher FHR1 or FHR1/FH ratio also associated with disease progression. Furthermore, renal transplantation in both IgAN and ADPKD patients was followed by reduction of FHR1 plasma levels (Medjeral-Thomas et al., 2017; Tortajada et al., 2017). In IgAN, the presence of complement activating surfaces, like the gd-IgA1-IC in circulation or mesangial deposits, makes FH competition critical, and unbalanced FHR1/FH ratio following decreased renal function may exacerbate AP dysregulation leading to progressive renal function impairment. Mesangial C3 deposition contributes to sustained FHR1/FH competition because activated fragments iC3b and C3dg are better ligands for FHR1 than for FH (Tortajada et al., 2013). Remarkably FHR1 has been observed in renal biopsies of IgAN with complement activating products, but correlations with disease progression were not clear (Paunas et al., 2017). In ADPKD there is likely no such complement activating surfaces. Consequently, associations between complement activity and ADPKD disease occurrence or severity have not been identified.

2.4. FHR5 levels and variants

FHR5 is also able to deregulate complement by competing with FH. Gain-of-function *CFHR5* mutations cause complement dysregulation and strongly associate with a type of familial C3 glomerulopathy, CFHR5 nephropathy. CFHR5 nephropathy shows phenotypic similarities with IgAN, like C3 glomerular deposits and mesangial proliferation (Goicoechea de Jorge et al., 2013). Rare *CFHR5* gene variants were identified In IgAN. Functional assays demonstrated the variants affect FHR5 surface binding regions to increase C3b binding capacity, suggesting the variant FHR5 impairs FH regulation, resulting in greater complement-mediated injury and IgAN susceptibility (Zhai et al., 2016). FHR5 protein plasma levels were higher in IgAN patients than controls in a UK and large Chinese IgAN cohort. In addition, serum FHR5 levels correlated with histologic markers of renal injury in both cohorts (Medjeral-Thomas et al., 2017; Zhu et al., 2018). In the larger, Chinese cohort, the differences in FHR5 levels between IgAN patients and controls was more pronounced and FHR5 levels correlated positively with proteinuria and hypertension, and negatively with eGFR

(Zhu et al., 2018). Glomerular FHR5 deposition was present in all IgAN cases from a series of glomerular disease biopsies, and was found in mesangial locations similar to IgA and C3 (Murphy et al., 2002). Recently, glomerular FHR5 deposition has been associated with IgAN progression and correlated with deposition of the C3 fragments C3b, iC3b, C3c and C3d as well as C5b-9, but not C4d. Importantly, glomerular FH staining was negative (Medjeral-Thomas et al., 2018). This is remarkable because it suggests FH competition takes place at the site of renal injury, where complement is intensely activated. Unexpectedly, the same study found no correlation of FHR1 glomerular staining with IgAN status. Together, these data demonstrate FHR5 is an important and independent player in AP dysregulation in IgAN.

The AP variants and risk factors described correlate with markers of IgAN severity, such as the Oxford classification, renal impairment, or the risk of progression to CKD. Considering the multiple risk factors and clinical heterogeneity associated with IgAN, a range of contributors and mechanisms may trigger AP dysregulation and modulate disease susceptibility and phenotype. Our appreciation of associations between FHR1 and FHR5 and IgAN coincided with insights in FHR protein biology, particularly the ability of FHR1 and FHR5 homodimers to interfere with the physiological actions of FH and deregulate complement activation (Tortajada et al., 2013; Goicoechea de Jorge et al., 2013). This allowed speculation of possible pathogenic mechanism linking variants in circulating and glomerular FHR proteins and IgAN incidence and severity; in response to a trigger, such as mesangial IgA1 deposition, imbalances or gain-of-function variants in the FHRs would increase alternative pathway activation and C3 cleavage leading to amplified complement-dependent inflammation and renal injury. Other associations with AP include partial deficiencies of regulators Factor I and Properdin, but these are anecdotal cases and the precise relationship with IgAN needs to be studied further (Maillard et al., 2015; Tortajada et al., 2017). In addition to AP dysregulation, pathogenesis since 17%–25% of IgAN patients show evidence of LP activation, we must consider the contribution of LP to mechanisms of IgAN (Maillard et al., 2015).

3. Lectin pathway in IgAN

The LP is activated by the binding of pattern recognition molecules (PRM) which include mannan-binding lectin (MBL), ficolins and collectins, to pathogen associated molecular patterns. The resultant complexes are then variably able to activate MBL-associated serine proteases (MASP) which consist of MASP-1, MASP-2 and MASP-3 (Axelgaard et al., 2013; Ma et al., 2013; Matsushita et al., 2000, 2002; Liu et al., 2005). MASP activation results in the formation of a C3 convertase, C4bC2b, and C3 activation (Garred et al., 2016). Immunohistological evidence of LP activation is the identification of C4d in the absence of C1q. Additional LP components found in renal biopsies include MBL, ficolins and MASP (Roos et al., 2006).

The LP is a plausible link between gd-IgA1 deposition and glomerular inflammation in IgAN pathogenesis. IgAN is characterised by disease flares following respiratory or gastrointestinal tract inflammation (Wyatt et al., 1987); both IgA and the LP are important mediators of innate immunity at these sites. Due to a deficiency in O-linked glycosylation, IgAN is associated with higher levels of IgA1 with exposed GalNac (Berthoux et al., 2012). GalNac may trigger LP activation due to interaction with ficolins (Thiel, 2007). *In vitro* data demonstrates IgA purified from pooled normal human serum binds MBL-MASP complexes. The presence of MBL-MASP leads to C3 and C4 deposition on immobilized IgA in the absence of CP activity, indicating MBL can bind pIgA and activate complement LP (Roos et al., 2001). Polymeric IgA fractions form IgAN patients can demonstrate strong MBL binding, but there is significant variability in IgAN patients and healthy controls (Roos et al., 2006). This *in vitro* data is supported by recent studies of genetic, serological and immunohistological LP variants in IgAN.

3.1. MBL variants

The influence of genetic and serology MBL variants in IgAN was investigated in a cohort of 749 IgAN patients and 489 controls from China (Guo et al., 2017). Circulating MBL levels are predominantly influenced by variants in exon 1, the promoter region, and the 5'-untranslated region of the *MBL2* gene (Madsen et al., 1995). These polymorphisms are in linkage disequilibrium, resulting in haplotypes associated with different MBL levels (Madsen et al., 1995, 1998; Madsen et al., 1994). The study found LYPB/LYPB and LXPA/LYPB *MBL2* genotypes were dominant determinants of deficient MBL levels (Guo et al., 2017). However, perhaps due to the large number of haplotypes limiting study power, no significant differences in haplotype frequencies between IgAN and controls were identified (Guo et al., 2017). Average plasma MBL levels were lower in controls than patients. Interestingly, associations between circulating MBL levels and IgAN severity were non-linear. First, MBL deficiency, defined as plasma levels less than 100 ng/ml, associated with poorer renal outcomes. About 25% MBL deficient (10 of 39) and 12% MBL sufficient (51 of 437) patients reached either 50% loss of eGFR or ESRD over median 47 months ($p = 0.01$) (Guo et al., 2017). This was statistically significant after adjustment for multiple risk factors known to influence IgAN progression. Second, markers of IgAN severity, in particular more severe proteinuria and the presence of cellular crescents, were also more common in the cohort of IgAN patients with MBL levels greater than 3540 ng/ml. Associations with high MBL levels were lost after multivariate adjustment, but may have retained statistical significance with longer duration of follow-up (Guo et al., 2017). Furthermore, there were more cases of prodromal infection and gross hematuria in the MBL deficient IgAN cohort. These suggest links between MBL deficiency, infection susceptibility, IgAN exacerbation frequency, and disease severity. Associations between IgAN severity and both high and low circulating MBL levels seem contradictory but are probably explained by multiple MBL-dependent mechanisms contributing to IgAN pathogenesis. For example, high circulating MBL levels might predispose individuals to LP triggered complement activation, renal injury and inflammation. And low circulating MBL levels might predispose to infections and associated IgAN exacerbations.

Associations between low MBL levels and IgAN severity have been replicated in other Chinese IgAN patient cohorts. Genetic sequencing of *MBL2* and *FCN2*, the gene that influences L-ficolin functional activity, in 50 Chinese IgAN patients revealed seven variants thought to influence protein expression. After adjustment for other ESRD risk factors, one *MBL2* variant, rs1800450, associated with ESRD in discovery and validation cohorts totaling 1007 IgAN patients. The at risk allele, rs1800450-A, is associated with reduced MBL levels; patients with homozygous AA at this SNP have no detectable circulating or glomerular deposited MBL, but more severe tubulointerstital renal damage and increased ESRD risk (Ouyang et al., 2019). Associations between progressive IgAN and low serum and urine MBL levels were identified in another study of 131 IgAN patients from a separate center in China (Shi et al., 2015).

Associations between IgAN and genetic and circulating MBL variants have not been demonstrated in non-Chinese cohorts. MBL polymorphism analysis in 160 IgAN patients and 74 controls from Italy did not demonstrate differences in allelic and genotypic frequencies. There were also no associations with disease severity (Pirulli et al., 2001). Albeit in small cohorts, circulating MBL levels did not associate with IgAN patients compared to healthy controls (Roos et al., 2006), other primary glomerulopathies, or disease severity in non-Chinese populations (Lhotta et al., 1999; Ohsawa et al., 2012). However, MBL is excreted in large quantities in the urine of patients with progressive IgAN (Roos et al., 2006). Explanations for these inconsistent MBL associations could include differences in cohort sizes, ethnicities, effects of reduced glomerular filtration on circulating MBL levels and definitions of progressive disease.

3.2. Variants in other lectin pathway proteins

Ficolin PRMs can interact with GalNac acetyl groups exposed on gd-IgA1 and therefore could, in theory, bind and localize complement activation (Garred et al., 2016; Kjaer et al., 2013). Analysis of 323 IgAN patients from London, 16% of whom were non-Caucasian ethnicity, demonstrated increased circulating M-ficolin, L-ficolin, MASP-1 and MAp19 levels in IgAN patients compared to healthy controls. Also, MASP-3 levels were reduced in IgAN and associated with progressive disease, both in the whole cohort and following immunosuppression treatment. Low MASP-3 and high MAp19 plasma levels also correlated with histology features of IgAN severity (Medjeral-Thomas et al., 2018). This study investigated the influence of estimated glomerular filtration rate (eGFR) loss on circulating lectin pathway protein levels. IgAN patients with preserved eGFR showed significant differences in plasma lectin levels compared to healthy controls, suggesting the differences were secondary to IgAN activity. Furthermore, despite a marked change in eGFR MASP-3 was not influenced by transplantation in IgAN and ADPKD patients (Medjeral-Thomas et al., 2018).

3.3. Lectin pathway immunohistology

Glomerular LP protein deposition associates with IgAN severity. Endo et al detected MBL and MASP-1 in renal biopsies from 24% of IgAN patients and 3% of other glomerulopathies (Endo et al., 1998). The deposited MBL/MASP-1 associated with glomerular C3b/C3c and C5b9 deposition, but did not correlate with serology markers of complement activation or clinical markers of IgAN severity. Roos et al demonstrated glomerular MBL, L-ficolin, MASP1/3 and C4d deposition in 25% of a cohort of 60 IgAN patients (Roos et al., 2006). Glomerular deposition associated with features of IgAN severity, specifically proteinuria, higher serum creatinine and renal failure (Roos et al., 2006). Espinosa et al identified glomerular C4d and absent C1q in 38.5% of 283 patients from Spain with IgAN (Espinosa et al., 2014). C3 deposition was identified in an equal proportion of C4d positive and C4d negative cases. It was argued that patients could be categorized based on glomerular evidence of either or both LP and AP activation. After multivariate analysis, positive glomerular C4d staining was a significant predictor of ESRD (Espinosa et al., 2014). This was replicated in a second Spanish cohort of 102 IgAN patients, in whom C4d deposition on renal biopsy associated with progression to doubling of serum creatinine (Zhu et al., 2014). Although not significant after multivariate analysis in this cohort, an interesting association was identified between glomerular C4d deposition, raised circulating FHR1 levels and IgAN progression that may be mechanistically informative (Zhu et al., 2014).

4. Terminal pathway

Terminal complement pathway activity may also be important to IgAN pathogenesis. As mentioned, immunohistochemistry analysis of IgAN patient biopsies identified glomerular C5b9 deposition (Rauterberg et al., 1987). Significant amounts of C5 to C9 proteins have been identified by proteomic analysis of micro-dissected glomeruli from IgAN kidney biopsies (Paunas et al., 2017). C5b9 deposition is associated with renal inflammation and progression of glomerulosclerosis in IgAN (Stangou et al., 2008). In a rat model of human mesangioproliferative glomerulonephritis, C5b9 induced mesangial cell apoptosis and the production of immune stimulatory signals, such as Il-6 and TGF-β1 (Qiu et al., 2014; Zhang et al., 2014), supporting a role for C5b9 in IgAN pathogenesis. Recently, *in vitro* evidence has emerged of a role for C5a, the anaphylatoxin released during terminal pathway activation in IgAN. Cultured human mesangial cell stimulation induced by IgA1 from pooled human serum is reduced by C5a receptor (C5aR) antagonists. Using a Sendai virus model of IgAN, C5aR knockout mice had less proteinuria, reduced glomerular C3 and IgA deposition and improved renal histology changes (Zhang et al., 2017).

5. Complement inhibition in IgAN

Due to the strong association between glomerular complement activation and IgAN, complement inhibitors are being tested in clinical trials (see clinicaltrials.gov for up-to-date trial information).

5.1. Factor B inhibitior: LNP023

Factor B (fB) is a fundamental protease in AP activation and amplification. AP dysregulation predisposes individuals to the development of numerous diseases including C3 glomerulopathy and IgAN (Maillard et al., 2015). Serum levels of fB are increased in patients with IgAN, which correlates with the activation of B-cells and the role of mucosal immunity in this disease (van den Wall Bake et al., 1988). Given B-cell activation may be involved in the production of Gd-IgA1 and its antibodies and complement AP activation is important in IgAN pathogenesis, blocking fB has potential pathophysiological importance. IgAN proteinuria reduction after 90 days of treatment with LNP023, an oral small molecule reversible fB inhibitor, is being tested in a phase IIa / IIb trial (NCT03373461).

5.2. Anti C5 monoclonal antibody: eculizumab

Eculizumab is a recombinant humanized monoclonal antibody that selectively inhibits C5, thereby preventing C5a release and formation of the membrane attack complex (MAC, C5b9). Eculizumab has been used in two young patients with progressive IgAN (Rosenblad et al., 2014; Ring et al., 2015). Eculizumab use was associated with temporary renal function and proteinuria stabilization, and disease progression on withdrawal. The patients had previously received other immunosuppressive treatments. Eculizumab has also been used in aggressive relapses of IgAN after kidney transplantation with little consistent clinical success, although this may be partially related to the timing of treatment. Interestingly, deposits of C3, C4d and C5 have been seen in the biopsies of these patients, demonstrating close relationships between complement and recurrent IgAN pathogenesis (Wyld and Chadban, 2016; Herzog et al., 2017).

5.3. MASP-2 inhibitor: OMS721

OMS721 is a monoclonal antibody to MASP-2 that led to significant reductions in proteinuria in 4 IgAN patients (Presented as abstract: Block GA, Whitaker S. Maintenance of remission following completion of OMS721 treatment in patients with IgA nephropathy (IgAN). J Am Soc Nephrol 2017; 28: 749-50. SA-PO278). A phase III, double-blind, randomized and placebo controlled study (NCT03608033) is in recruitment and aiming to evaluate the safety and efficacy of OMS721 in patients with IgAN and more than 1 g/day proteinuria (Smedbraten et al., 2016).

5.4. Anti-C3: compstatin and APL-2

Compstatin inhibits the activation of C3. As described above, inhibitors of C3 activation may be potential candidates for IgAN treatment (Rops et al., 2018; Yamada et al., 2017). Specific pathophysiological justification is provided by the finding that C3 (and C5) receptor antagonists prevent the proliferation of cultured human mesangial cell stimulated by IgA1 (Zhang et al., 2017). Reduction in IL-6 up-regulation, a key mediator of mesangial cell activation and immune cell glomerular filtration, was also observed. APL-2 is a pegylated derivative of compstatin that binds C3 and prevents cleavage to C3a and C3b by C3 convertase. APL-2 is being evaluated in a phase 2 study as treatment for patients with IgAN, lupus nephritis, primary membranous nephropathy or C3 glomerulopathy (NCT03453619).

5.5. Anti-C5a receptor inhibitor: CCX168 (Avacopan)

Avacopan is a small molecule that antagonizes complement-dependent inflammation through its binding to the C5aR. C5a is an important inflammatory mediator in systemic vasculitis, for which Avacopan seems to be an effective alternative to glucocorticoids (Jayne et al., 2017). The aforementioned mesangial cell and animal model experiments suggest C5aR inhibition could be effective in IgAN (Zhang et al., 2017). A Phase II study (NCT02384317) to evaluate the safety, tolerability and efficacy of CCX168 in reducing proteinuria in IgAN patients receiving maximum tolerated RAAS blockade is being analyzed.

5.6. C5 suppression by a RNA interference (RNAi): ALN-CC5 (Cemdisiram)

Cemdisiram is a synthetic RNAi designed to suppress liver production of C5, which may reduce terminal complement pathway activation and subsequent inflammation. A Phase II, double-blind, randomized and placebo controlled study (NCT03841448) is in recruitment and aims to evaluate the safety and efficacy of Cemdisiran in patients with IgAN and more than 1 g/day proteinuria.

Successful application of these agents will depend on accurately selecting patients for who the benefit of complement inhibition outweighs the risks. Such personalized approaches to treatment decisions are particularly important in IgAN because of its wide range of clinical outcomes. We need to reliably identify cases with ongoing complement activation. We also need to identify theresponsible complement pathways and proteins. This necessitates the development of biomarkers of specific complement activation. We next need to identify cases with ongoing glomerular inflammation. Although the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines consider that proteinuria greater than 1 g/day justifies treatment (Floege et al., 2019), proteinuria in IgAN may be the result of sclerotic hyperfiltration and tubular damage. Therefore, microscopic haematuria may clarify disease activity and ongoing inflammation (Sevillano et al., 2017). This is exemplified by IgA1 protease treatment that decreases IgA1 deposition, inflammation, mesangial expansion, and haematuria without significantly influencing proteinuria (Lechner et al., 2016). Additionally, histology can identify ongoing inflammation, such as with the presence of endocapillary hypercellularity and cellular crescents. However, using the Oxford MEST-C score to make therapeutic decisions is currently unproven (Trimarchi et al., 2019). This is being addressed with the Treatment of IgA Nephropathy According to Renal Lesions (TIGER) study (NCT031888887) (Coppo, 2018). Additionally, glomerular and circulating markers of complement activation may become useful biomarkers of ongoing inflammation that identify patients who would benefit from immunosuppression, even if therapeutic complement inhibition is unavailable.

6. Future research

Complement is in the spotlight of IgAN research. Unsurprisingly given the complexity and heterogeneity of IgAN pathogenesis, a number of questions require clarification.

i) Where is the specific site of complement activation? *In vitro* assays showed IgA can trigger both LP and AP, and circulating gd-IgA1-IC contain C3 the products iC3b, C3c and C3dg (Hiemstra et al., 1987; Roos et al., 2001; Knoppova et al., 2016; Tomana et al., 1999). However, it is not clear whether pathogenic complement activation occurs in the fluid phase on circulating complexes, in the glomeruli after mesangial deposition, or both. This may help place complement activation in the four-hit model of IgAN pathogenesis.
ii) A unique characteristic of IgAN is the presence of gd-IgA1-IC deposits in the mesangium, but does the O-glycan deficiency have a role in the activation of AP and LP? The results of experiments using laboratory IgA preparations were controversial. Removal of sialic acid or N-glycans from IgA1 and IgA2 isotypes with specific enzymes resulted in enhanced AP C3b fixation. This was not seen for O-linked galactose and galactosamine, which are important components of IgAN glomerular deposits (Nikolova et al., 1994). Conversely, another study using culture-generated deglycosylated IgA showed weaker C3b deposition (Zhang and Lachmann, 1994).
iii) How does complement cause glomerular damage in IgAN? It has been shown that deposition of C5b9 induces mesangial cell stress and that C3a stimulates mesangial cells leading to secretory phenotypes (Stangou et al., 2008; Qiu et al., 2014; Zhang et al., 2014; Wan et al., 2007). However, it is unknown if complement additionally alters glomerular cell responses to pathogenic gd-IgA1-IC. Accordingly, whether inflammatory responses to gd-IgA1-IC are amplified in individuals with underlying imbalances of complement regulation needs investigation.
iv) Which complement pathways are pathogenically dominant in IgAN? Why is LP activation only seen in some patients? Discrepancies in pathway associations may reflect the heterogeneity in IgAN clinical presentations and outcomes. In addition to looking for correlates with clinical outcome such as ESRD, given the increasing availability of inhibitors of specific complement pathways, it will also be important to establish whether particular LP and AP activation correlate with active glomerular inflammation. Although individual studies have looked at endocapillary hypercellularity in patients with complement variants such as raised FHR5 (Medjeral-Thomas et al., 2017), how LP and AP activity correlate with histology evidence of inflammation or scarring is unclear.
v) How does IgAN severity associate with both glomerular evidence of LP activity, raised circulating LP protein levels including MBL, and MBL deficiency? Predicting how reduced MASP-3 levels associate with IgAN severity is difficult because the physiological roles of MASP-3 are unclear. Although MASP-3 binds lectin PRMs, it cannot cleave complement convertases (Ouyang et al., 2019), and inhibits LP activation when added to MBL-MASP complexes (Shi et al., 2015; Pirulli et al., 2001). Conversely, MASP-3 can cleave profactor to fD thereby potentially linking lectin and alternative complement pathways.
vi) Which FHR1 and FHR5 mechanisms drive IgAN progression? It has been proposed that FHR1 and FHR5 competition with FH ligands cause AP dysregulation and influence IgAN and other complement-associated diseases. However, other mechanisms may be important. *In vitro* C3b-bound FHR4 and FHR5 have been shown to enhance complement activation by scaffolding AP convertase formation C3b (Hebecker and Jozsi, 2012; Csincsi et al., 2015). Also, FHR proteins may interfere with the uptake and metabolism of circulating or deposited C3, perhaps bound to gd-IgA1-IC, thus potentiating complex immunogenicity and amplifying inflammation.

7. Conclusion

IgAN remains a common disease without a treatment. Glomerular complement activation is strongly associated with IgAN (Table 1) and may be the dominant driver of renal injury. If this is the case complement inhibition may emerge as an effective method of preventing or reducing glomerular injury in IgAN. The outcome of trials of complement inhibitors in IgAN is eagerly awaited.

Declaration of Competing Interest

None.

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