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EDITORIAL

C4d deposits in IgA nephropathy: where does complement activation come from?

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Introduction

Among the conundrums surrounding immunoglobulin A nephropathy (IgAN) are its variable course and which biomarkers are best for predicting outcomes and need for treatment in potentially progressive patients [1]. The pathogenesis of IgAN is thought to be due to several factors ("hits") [2] which play a permissive role in the development of IgA deposits that have an inflammatory potential, leading to glomerular damage. The production of galactose-deficient IgA1 (Gd-IgA1) as a result of defective galactosylation of *O*-linked glycans typical of the IgA1 molecule is increased in patients with IgAN, but also in healthy relatives, suggesting the need of additional hits. Gd-IgA1 binds to soluble CD89 (Fc alphaRI, myeloid IgA Fc receptor) and forms IgA1-CD89 complexes which interact with transferrin receptors (CD71/TfR1) and transglutaminase 2 (TGase2) in mesangial cells, thereby activating mediators and matrix production [3]. Moreover, Gd-IgA1 induces antiglycan autoantibody synthesis, leading to macromolecular Gd-IgA1(CD89)/IgG or IgA anti-Gd-IgA1 immune complex formation and renal deposition [2]. However, renal damage and progression towards sclerosis is highly variable, hence the presence of a crucial additional hit is envisaged. Complement activation is an attractive candidate for the pivotal hit in IgAN as the cue for triggering the inflammation and progression that is responsible for the variable clinical outcome.

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In a recent article in *Pediatric Nephrology*, Cabral Gonçalves Fabiano et al. reported that a sign of complement activation, namely the presence of the complement split product C4d in mesangial deposits, may predict progression of renal damage in children with IgAN [4], thus expanding to pediatric patients what has been reported in adults [5]. This report adds another brick to the evidence accumulated in recent years on the crucial role of complement in the pathogenesis and progresson of IgAN [6, 7]. However, the mystery which attracts most interest at this moment is how complement activation leading to C4d deposition is triggered in IgAN. The answer to this question may be relevant for future therapeutic choices. In this paper I review some old and some new data and suggest a number of hypotheses to be tested in future studies.

Complement activation pathways

Complement component 3 (C3) is activated by the action of C3 convertase, which cleaves C3 into two elements, C3b and C3a [6, 7]. Activated C3 interacts with pathogens, immune complexes and/or cell receptors. After this binding, C3 is degraded to iC3b by the inhibitor molecules factor I (FI) and factor H (FH), which favor the phagocytic process with clearance of the bound material. C3 activation can result from C1q binding to IgG (IgG1, IgG2, IgG3) or IgM that contains circulating immune complexes; this process initiates the complement classical pathway. Activated C1q (C1qrs) cleaves C2 and C4, leading to the formation of the C3 convertase C4b2a.

C3 can be activated by the alternative pathway [8], which is initiated as a result of a spontaneous and continuous hydrolysis of C3 (tickover process). This results in the generation of C3b which can react with complement-binding surface molecules (e.g. in bacteria) and interact with factor B (FB) and

factor D, leading to the formation of C3bBb convertase. This labile convertase is stabilized by properdin which favors the binding of FB and C3b.

Finally, C3 can be generated via the lectin pathway by pattern recognition molecules, i.e. carbohydrates expressed on microorganisms or altered tissues [9]. The lectin pathway includes two collectins [mannose-binding lectin (MBL) and collectin-LK] and the three ficolins (ficolin-1, -2 and -3) and MBL-associated proteases (MASP-1,-2 and -3), which enable activation of C4 and C2, leading to the formation of C4bC2a, the same convertase found in the classical complement pathway.

The complement system is regulated by a series of factors acting as inhibitors in both fluid phase and solid phase. These include FH and FI, which regulate the alternative pathway, and others which regulate all of the complement pathways at the cellular membrane level, including decay accelerating factor (CD55), membrane cofactor protein (CD46) and CD59 [6, 7]. The lectin pathway has two specific MASPs (MAp44 and MAp19) that serve as natural endogenous competitive inhibitors [9, 10].

The C3 convertases produced by activation of one of these three pathways lead to the generation of C3a (anaphylotoxin) and C3b, which forms the C5 convertase (4bC2aC3b or C3bBbC3b). The common terminal complement pathway is then activated, with generation of C5a (anaphylotoxin) and C5b, followed by the final cascade C5b, C6, C7, C8, C9 (C5b-9 or membrane attack complex). C5b-9 can induce cell lysis, but low amounts of C5b-9 are also very active in enhancing cytokines and chemokines, while C3a and C5a are highly chemotactic fragments that upregulate adhesion molecules and phagocytic cells. Complement activation is known to pay a major role in inflammatory reactions in many immune-mediated diseases.

Complement activation in IgA nephropathy

Complement activation has been suspected to be involved in the pathogenesis of IgAN since the detection of C3 co-deposits with IgA in the mesangial area in up to 90% of cases. Several studies suggest that C3 bound to IgA confers a particular nephrotoxicity to the IgA1-containing immune material, leading to the hypothesis that this step is the crucial hit in the pathogenetic event cascade of IgAN [8, 9, 11]. A different efficacy of complement activation may modulate the glomerular inflammatory reaction and the final tissue damage, driving different renal outcomes. Hence, several studies have been undertaken to investigate the origin of C3 in the presence of immune material-containing IgA.

Gd-IgA1 or aggregated IgA1 can bind to mesangial cells and directly trigger the secretion of C3, C3a formation and activation of C3a receptors on mesangial cells [11]. However, in addition to this in situ activation, a systemic complement activation has been suggested by several studies, including a negative correlation between circulating C3 and mesangial C3 deposition [12]. C3 levels in Caucasian patients with progressive IgAN are not noticeably reduced, while in Chinese and Japanese patients slightly reduced levels of complement (<90 mg/dl) have been detected in similar cases [12, 13]. The ratio between IgA levels (frequently increased in patients with IgAN) and C3 levels (seldom changed and then only slightly decreased) has been reported to be of prognostic value in adults and children [14].

In spite of a mild and often undetectable decrease in C3 levels in IgAN, increased breakdown products have been found in the circulation [15]. Activated C3 generates the terminal end-products iC3b and C3d, and these have been found to be particularly increased in patients with severe pathology lesions or with progressive forms of IgAN [15, 16]. Activated complement factors bound to IgA can be detected by testing their binding to bovine conglutinin (KIgAIC) [17]. In previous studies conducted at our institution we detected increased levels of complement-fixing KIgAIC in patients with active IgAN, with the levels of KIgAIC being significantly correlated with C3d levels [18]. Of interest, in a study of patients with progressive IgAN treated with plasma exchange, the clinical benefits corresponded with a decrease in KIgAIC and complement breakdown products [19].

What triggers complement activation in IgAN?

Alternative complement pathway and IgAN

Renal co-deposits of properdin and FH are reported in up to 90% of IgAN cases [7, 15]. Complement inhibiting factors acting in fluid phase according to the hypothesis of systemic activation have been investigated in patients with IgAN. In Asiatic patients an association was reported between C3 and FH levels, suggesting an active regulation of the alternative complement pathway even in cases of subclinical activation [12, 13].

A protective effect against the development of IgAN has been detected in subjects with deletion of complement factor H-related protein 1 (CFHR1) and 3 (CFHR3) and a single nucleotide polymorphism, rs6677604 (Chr1q32), which is a proxy for the deletion of CFHR1/3; both were found to be associated with a low risk of IgAN [20]. The lack of CFHR1 and CFHR3 products increases the activity of FH for defective competition [6], thus limiting alternative complement pathway activation. In a large Chinese cohort of IgAN patients, variants of FH were found to be associated with increased C3 mesangial deposits, confirming a role for genetically conditioned FH levels and complement activation [21]. However, the study failed to detect a predictive value of FH or C3 mesangial deposition on IgAN outcome.

A positive correlation between C4d and regulatory proteins (FH, C4-binding protein and C1 inhibitor) has been reported, suggesting a regulation of in situ complement activation of the lectin pathway in patients with IgAN [22]. In the event of complement activated by IgA containing immune material on the surface of mesangial cells, a defective cell-surface complement regulation by locally acting factors, including CD55, CD46 and CD59, might be implicated [6, 7]. These regulators act on activating surfaces of bacterial cell-wall glycans, but also on IgA macromolecular immune aggregates [11]. Without their inhibitory effect, an amplification loop develops in the presence of Factor D and properdin, leading to the accumulation of C3bBb, the alternative pathway C3 convertase. We recently observed defective CD46 expression in peripheral mononuclear cells of patients with progressive IgAN (unpublished data), leading to the hypothesis of a modulation by infiltrating mononuclear cells or resident mesangial cells favoring harmful inflammatory complement-mediated pathways in patients with progressive IgAN.

Lectin pathway in IgAN

Activation of C3 can be the result of activation of the lectin pathway, which has been supposed to be activated in patients with IgAN who show renal deposition of MBL, ficolins, MASP and C4d, in the absence of C1q [9, 23]. The prognostic value of the presence and intensity of C3 deposits for outcome has been reported by some but not all authors [12]. The detection of glomerular C4d deposits has been proposed by Espinosa et al. as an early biomarker for progressive IgAN in a cohort of children and adults [5]. The new data in children reported by Cabral Gonçalves Fabiano et al. [4] add further relevance to this histological biomarker along the whole age spectrum. Of interest, serum proteomic analysis detected increased levels of C4a desArg (a breakdown product of C4d) in patients with severe renal pathology and progressive disease [24].

What triggers the lectin pathway leading to C4d deposits in patients with IgAN?

C4d is the result of C4 cleavage and persists in tissues because it covalently binds to surrounding molecules. Hence, C4d is a long-lasting marker of complement activation: it does not represent active pathway stimulation, but rather a previous activation which might be associated with permanent tissue damage. In transplanted kidneys, C4d is a good marker of anti-donor antigen antibodies that reacted with graft endothelium and activated the classical complement pathway. In several glomerular diseases, C4d staining is a useful diagnostic factor because it is a sign of antibody-mediated or immune complex-induced glomerulonephritis [25]. The coincidence of C4d with C1q deposits and immunoglobulins is typical of classical complement pathway activation in lupus nephritis. Conversely, in patients with IgAN, C4d deposits are not associated with C1q and hence are thought to be activated by the lectin pathway.

Which activator of the lectin pathway leads to C4d deposits? Several attempts have been made to specifically identify factors activating MBL in IgAN. To date, however, no genetically conditioned modified synthesis of MBL has been found [7]. It is of interest that low levels of MAp44, a MASP inhibitor of the lectin pathway, favor increased innate immunity and shorter renal graft survival [10]. However, this modulating factor has not been tested in IgAN.

Serum MBL levels are increased in 30% of IgAN patients, and MBL is excreted in large amounts in the urine of patients with progressive IgAN [15, 22]. These findings may suggest a role for infections, since bacterial cell-wall glycans with exposed D-mannose or *N*-acethylglucosamine residues are known activators of the lectin pathway, and infections trigger innate immunity in IgAN [26], thereby activating toll-like receptor signaling in peripheral blood mononuclear cells. However, the search for specific pathogens in renal biopsies of patients with IgAN has been inconclusive. Recent studies have indicated the presence of specific tonsillar and intestinal microbiota in patients with IgAN, possibly leading to a hypothesis of a selective lectin pathway activation due to altered host mucosal microbiota.

IgA molecules, particularly polymeric IgA molecules, which are increased in patients with IgAN, bind in vitro to MBL by an interaction with sugars, and this interaction is blocked by pre-incubation with D-mannose or *N*-acetylglucosamine [9]. MBL binding to IgA triggers the lectin pathway, resulting in activation of C4 and C3 [9]. It is tempting to speculate a role for aberrantly glycosylated IgA1 in these patients. However, galactose deficiency leading to GdIgA1, which is considered the clue initiating the pathogenesis of IgAN, affects *O*-linked sugars which do not contain mannose or *N*-acetylglucosamine, the sugars needed for lectin pathway activation. Mass spectrometric analysis has revealed the presence of complex biantennary *N*-glycans rich in mannose and terminal *N*-acetylglucosamine in IgA molecules. The IgA1 subclass contains two conserved *N*-glycosylation sites per heavy chain: one at residue N263 in the CH2 domain and the other at N459 in the tailpiece [27]. IgA2 has an additional two or three conserved *N*-glycans. Moreover, the joining chain in the dimeric IgA contains a single *N*-glycan, and the secretory component in the secretory IgA (sIgA) variant is heavily *N*-glycosylated. In patients with IgAN some glomerular staining of sIgA has been detected in coincidence with MBL and C4d [7]. However, the sIgA deposits are much less intense than the IgA1 ones.

No difference between IgAN patients and healthy controls has been reported for the binding of serum IgA to lectins specific for *N*-acethylglucosamine or terminal D-galactose of

N-linked moieties [28, 29]. To date, ours is the only group to report a significantly increased binding of IgA isolated in chromatographic fractions from patients with IgAN to Canavalia ensiformis (ConA), which is specific for mannose residues [29], suggesting a possible truncation of *N*-glycans in serum IgA of patients. No modification of N-glycans on IgG was detected. The increased exposure of truncated *N*-glycans was found to modify the nitric oxide synthesis and integrin expression of mesangial cells [30]. Moreover, *N*-glycans modulate the hepatic clearance of IgA molecules [31]. It is of interest that *N*-glycosylated residues bind to FC alpha receptor (CD89) and that the binding between Gd-IgA1 and soluble CD89 is supposed to be critical for the development of IgAN [3]. However, this binding of IgA1-CD89 was found not to be affected by *N*-glycosylated residues of IgA1 [27]. Some studies have investigated a possible role for the *N*-glycans of IgA1 in complement activation. At variance with *O*-glycans, *N*-glycan in vitro enzymatic removal does not influence the C3b alternative pathway activation [32]. The specific role of the *N*-glycans of IgA from patients with IgAN in activating the lectin complement pathway deserves further investigation.

Conclusion

In conclusion, several datasets indicate that C4d is a valuable biomarker for progressive IgAN, and it is likely to be used in future pathology classifications of IgAN. In spite of a series of studies, no consistent results have identified the mechanisms triggering lectin pathway activation in this disease. The candidate factors include selected pathogens with surface sugars that react with MBL or truncated and mannose-exposing *N*-glycans of the IgA1 molecules, as well as defective lectin pathway regulatory factors. Further studies in this fascinating area are needed and are likely to provide new therapeutic approaches for children with IgAN.

Compliance with ethical standards

Conflict of interest None to declare.

References

1. Coppo R (2016) Biomarkers and targeted new therapies for IgA nephropathy. Pediatr Nephrol. doi:10.1007/s00467-016-3390-9
2. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, Wyatt RJ, Scolari F, Mestecky J, Gharavi AG, Julian BA (2011) The pathophysiology of IgA nephropathy. J Am Soc Nephrol 22:1795–1803
3. Lechner SM, Papista C, Chemouny JM, Berthelot L, Monteiro RC (2016) Role of IgA receptors in the pathogenesis of IgA nephropathy. J Nephrol 29:5–11
4. Cabral Gonçalves Fabiano R, Almeida Araujo S, Alves Bambirra E, Araujo Oliveira E, Simoes e Silva AC, Brant Pinheiro SV (2017) Mesangial C4d deposition may predict progression of kidney disease in pediatric patients with IgA nephropathy. Pediatr Nephrol. doi:10.1007/s00467-017-3610-y
5. Espinosa M, Ortega R, Sánchez M, Segarra A, Salcedo MT, González F, Camacho R, Valdivia MA, Cabrera R, López K, Pinedo F, Gutierrez E, Valera A, Leon M, Cobo MA, Rodriguez R, Ballarín J, Arce Y, García B, Muñoz MD, Praga M, Spanish Group for Study of Glomerular Diseases (GLOSEN) (2014) Association of C4d deposition with clinical outcomes in IgA nephropathy. Clin J Am Soc Nephrol 9:897–904
6. Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, Novak J (2015) Current understanding of the role of complement in IgA nephropathy. J Am Soc Nephrol 26:1503–1512
7. Daha MR, van Kooten C (2016) Role of complement in IgA nephropathy. J Nephrol 29:1–4
8. Hiemstra PS, Gorter A, Stuurman ME, Van Es LA, Daha MR (1987) Activation of the alternative pathway of complement by human serum IgA. Eur J Immunol 17:321–326
9. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR (2001) Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol 167: 2861–2868
10. Smedbråten J, Mjøen G, Hartmann A, Åsberg A, Rollag H, Mollnes TE, Sandvik L, Fagerland MW, Thiel S, Sagedal S (2016) Low level of MAp44, an inhibitor of the lectin complement pathway, and long-term graft and patient survival; a cohort study of 382 kidney recipients. BMC Nephrol 17:148
11. Schmitt R, Ståhl AL, Olin AI, Kristoffersson AC, Rebetz J, Novak J, Lindahl G, Karpman D (2014) The combined role of galactose-deficient IgA1 and streptococcal IgA-binding M protein in inducing IL-6 and C3 secretion from human mesangial cells: implications for IgA nephropathy. J Immunol 193:3173–26
12. Kim SJ, Koo HM, Lim BJ, Oh HJ, Yoo DE, Shin DH, Lee MJ, Doh FM, Park JT, Yoo TH, Kang SW, Choi KH, Jeong HJ, Han SH (2012) Decreased circulating C3 levels and mesangial C3 deposition predict renal outcome in patients with IgA nephropathy. PLoS One 7:e40495
13. Suzuki H, Ohsawa I, Kodama F, Nakayama K, Ohtani A, Onda K, Nagamachi S, Kurusu A, Suzuki Y, Ohi H, Horikoshi S, Tomino Y (2013) Fluctuation of serum C3 levels reflects disease activity and metabolic background in patients with IgA nephropathy. J Nephrol 26:708–715
14. Mizerska-Wasiak M, Małdyk J, Rybi-Szumińska A, Wasilewska A, Miklaszewska M, Pietrzyk J, Firszt-Adamczyk A, Stankiewicz R, Bieniaś B, Zajączkowska M, Gadomska-Prokop K, Grenda R, Pukajło-Marczyk A, Zwolińska D, Szczepańska M, Turczyn A, Roszkowska-Blaim M (2015) Relationship between serum IgA/C3 ratio and severity of histological lesions using the Oxford classification in children with IgA nephropathy. Pediatr Nephrol 30: 1113–1120
15. Hastings MC, Moldoveanu Z, Suzuki H, Berthoux F, Julian BA, Sanders JT, Renfrow MB, Novak J, Wyatt RJ (2013) Biomarkers in IgA nephropathy: relationship to pathogenetic hits. Expert Opin Med Diagn 7:615–627
16. Zwirner J, Burg M, Schulze M, Brunkhorst R, Götze O, Koch KM, Floege J (1997) Activated complement C3: a potentially novel predictor of progressive IgA nephropathy. Kidney Int 51:1257–1264
17. Coppo R, De Marchi M, Aprato A, Roccatello D, Messina M, Segoloni G, Camussi G, Alloatti S, Giacchino F, Carbonara AO, Vercellone A, Piccoli G (1980) A new test for IgA containing immune complexes or aggregated IgA: its application to Berger and Schönlein-Henoch nephritis. Proc Eur Dial Transplant Assoc 17: 667–672
18. Coppo R, Giacchino F, Alloatti S, Quarello F, Segoloni G, Bossi P, Vercellone A, Piccoli G (1979) Are circulating immune complexes

and complement breakdown products useful for the detection of disease activity in nephrology? Proc Eur Dial Transplant Assoc 16:709–710
19. Coppo R, Basolo B, Roccatello D, Giachino O, Lajolo D, Martina G, Rollino C, Amore A, Costa M, Piccoli G (1985) Immunological monitoring of plasma exchange in primary IgA nephropathy. Artif Organs 9:351–360
20. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, Fasel D, Lata S, Prakash S, Shapiro S, Fischman C, Snyder HJ, Appel G, Izzi C, Viola BF, Dallera N, Del Vecchio L, Barlassina C, Salvi E, Bertinetto FE, Amoroso A, Savoldi S, Rocchietti M, Amore A, Peruzzi L, Coppo R, Salvadori M, Ravani P, Magistroni R, Ghiggeri GM, Caridi G, Bodria M, Lugani F, Allegri L, Delsante M, Maiorana M, Magnano A, Frasca G, Boer E, Boscutti G, Ponticelli C, Mignani R, Marcantoni C, Di Landro D, Santoro D, Pani A, Polci R, Feriozzi S, Chicca S, Galliani M, Gigante M, Gesualdo L, Zamboli P, Battaglia GG, Garozzo M, Maixnerová D, Tesar V, Eitner F, Rauen T, Floege J, Kovacs T, Nagy J, Mucha K, Pączek L, Zaniew M, Mizerska-Wasiak M, Roszkowska-Blaim M, Pawlaczyk K, Gale D, Barratt J, Thibaudin L, Berthoux F, Canaud G, Boland A, Metzger M, Panzer U, Suzuki H, Goto S, Narita I, Caliskan Y, Xie J, Hou P, Chen N, Zhang H, Wyatt RJ, Novak J, Julian BA, Feehally J, Stengel B, Cusi D, Lifton RP, Gharavi AG (2014) Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet 46:1187–1196
21. Zhu L, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, Shi SF, Liu LJ, Yu F, Zhao MH, Novak J, Gharavi AG, Zhang H (2015) Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA nephropathy. J Am Soc Nephrol 26:1195–1204
22. Endo M, Ohi H, Satomura A, Hidaka M, Ohsawa I, Fujita T, Kanmatsuse K, Matsushita M, Fujita T (2001) Regulation of in situ complement activation via the lectin pathway in patients with IgA nephropathy. Clin Nephrol 55:185–191
23. Ohsawa I, Ishii M, Ohi H, Tomino Y (2012) Pathological scenario with the mannose-binding lectin in patients with IgA nephropathy. J Biomed Biotechnol 2012:476739
24. Sogabe A, Uto H, Kanmura S, Nosaki T, Oyamada M, Tokunaga K, Nishida C, Fukumoto M, Oku M, Nishimoto K, Takenouchi S, Ido A, Shimada Y, Tsubouchi H (2013) Correlation of serum levels of complement C4a desArg with pathologically estimated severity of glomerular lesions and mesangial hypercellularity scores in patients with IgA nephropathy. Int J Mol Med 32:307–314
25. Sethi S, Nasr SH, De Vriese AS, Fervenza FC (2015) C4d as a diagnostic tool in proliferative GN. J Am Soc Nephrol 26:2852–2859
26. Rollino C, Vischini G, Coppo R (2016) IgA nephropathy and infections. J Nephrol 29:463–468
27. Gomes MM, Wall SB, Takahashi K, Novak J, Renfrow MB, Herr AB (2008) Analysis of IgA1 N-glycosylation and its contribution to FcalphaRI binding. Biochemistry 47:11285–11299
28. Allen AC, Harper SJ, Feehally J (1995) Galactosylation of *N*- and *O*-linked carbohydrate moieties of IgA1 and IgG in IgA nephropathy. Clin Exp Immunol 100:470–474
29. Amore A, Cirina P, Conti G, Brusa P, Peruzzi L, Coppo R (2001) Glycosylation of circulating IgA in patients with IgA nephropathy modulates proliferation and apoptosis of mesangial cells. J Am Soc Nephrol 12:1862–1871
30. Peruzzi L, Amore A, Cirina P, Trusolino L, Basso G, Ricotti E, Emancipator SN, Marchisio PC, Coppo R (2000) Integrin expression and IgA nephropathy: in vitro modulation by IgA with altered glycosylation and macromolecular IgA. Kidney Int 58:2331–2340
31. Rifai A, Fadden K, Morrison SL, Chintalacharuvu KR (2000) The *N*-glycans determine the differential blood clearance and hepatic uptake of human immunoglobulin (Ig)A1 and IgA2 isotypes. J Exp Med 191:2171–2182
32. Nikolova EB, Tomana M, Russell MW (1994) The role of the carbohydrate chains in complement (C3) fixation by solid-phase-bound human IgA. Immunology 82:321–327