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Role of IgA receptors in the pathogenesis of IgA nephropathy

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Keywords

IgA glycosylation; IgA nephropathy; gluten; IgA receptors, CD89, Transferrin receptor.

Abstract

Immunoglobulin A (IgA) nephropathy (N) or Berger's disease is the most common form of primary glomerulonephritis in the world and one of the first causes of end-stage renal failure. IgAN is characterized by the accumulation of immune complexes containing polymeric IgA1 in mesangial areas. The pathogenesis of this disease involves the deposition of polymeric and hypogalactosylated IgA1 (Gd-IgA1) in the mesangium. Quantitative and structural changes of Gd-IgA1 play a key role in the development of the disease due to functional abnormalities of two IgA receptors: the Fc α RI (CD89) expressed by blood myeloid cells and the transferrin receptor (CD71) on mesangial cells. Abnormal Gd-IgA1 induces release of soluble CD89, which participates in the formation of circulating IgA1 complexes. These complexes are trapped by CD71 that is overexpressed on mesangial cells in IgAN patients together with the crosslinking enzyme transglutaminase 2 allowing pathogenic IgA complex formation *in situ* and mesangial cell activation. A humanized mouse model expressing IgA1 and CD89 develops IgAN in a similar manner as patients. In this model, a food antigen, the gliadin, was shown to be crucial for circulating IgA1 complex formation and deposition, which could be prevented by gluten free diet. Identification of these new partners opens new therapeutic approaches for IgAN treatment.

Immunoglobulin A (IgA)

IgA is a relatively “unique” antibody isotype in humans due on one hand to their heterogeneity in molecular forms, in subclasses and in glycosylation, and on another hand to the unexpected poor participation of serum IgA in systemic immune responses [1]. IgA is by far the most abundantly produced isotype in humans, which are differentially distributed between the systemic and mucosal immune system. More IgA is produced per day (66 mg/kg/day) than all other classes combined [2], notably at epithelial sites where most is lost daily within exocrine secretions as mucosal surface encompasses more than 400 m². Serum IgA, the second most abundant isotype in the circulation, are mainly monomers derived from bone marrow plasma cells [1], whereas secretory IgA are synthesized as dimers by local plasma cells before being transported to mucosal surfaces through epithelial cells by the polymeric Ig receptor [3]. IgA displays a T-shaped structure, which differs from the common Y-shape of other Ig [4]. IgA is divided into closely related subclasses, IgA1 and IgA2, which basically differ by the absence of a thirteen-amino acid sequence in the hinge region of the IgA2 molecule [5]. This difference explains the resistance of IgA2 against the action of bacterial proteases (i.e. from *Streptococcus* mutants, *Neisseria meningitidis* and *Haemophilus influenzae*) and may underlie the predominance of IgA2 in mucosal secretions [5]. Interestingly, the IgA system differs substantially between species studied that are man, mice and rats. While two IgA subclasses are recognized in humans, only one class exists in mice and rats [6]. Serum IgA is mostly monomeric in humans, and polymeric in mice. Clearance *via* the hepatobiliary route plays an important role in mice, but not in humans [1]. In serum, IgA (mainly monomeric and of the IgA1 subclass) constitutes one fifth of the total Ig pool due to a rapid catabolism (half life: 3-6 days). IgA is the most glycosylated form of Ig, with carbohydrates representing about 6% of its content. Unlike IgA2, the heavy chains of IgA1 molecules contain a unique insertion in its hinge-region segment between the first and second constant region domains. This hinge region has a high content of serine and threonine residues, which are the sites of attachment of up to five O-linked glycan chains consisting of *N*-acetylgalactosamine with a β 1,3-linked galactose and sialic acids [7]. Sialic acid can also be attached to *N*-acetylgalactosamine by an α 2,6 linkage. It is noteworthy, however, that the carbohydrate composition of these O-linked glycans in the hinge region of serum IgA1 is heterogenous, the commonest forms including *N*-acetylgalactosamine-galactose disaccharide, and its mono- and di-sialylated variants.

Role of IgA receptors in homeostasis and immune protection

Serum monomeric IgA (mIgA) is a poor player in systemic immune responses. It plays rather a paradoxical role in immunity with its involvement in immune inhibition but also as a pathogenic actor in inflammatory diseases depending on the type and structure of IgA. The major role of serum mIgA in physiology is a powerful anti-inflammatory effector towards immune system. It has been demonstrated by several groups for more than two decades that in the absence of antigen, serum IgA down-regulates IgG-mediated phagocytosis, chemotaxis, bactericidal activity, oxidative burst activity, and cytokine release [8–14]. The most striking supporting evidence for the inhibitory role of serum mIgA comes from patients with selective IgA deficiency [15]. In these patients, both IgA1 and IgA2 are usually markedly reduced or absent. In addition to increased infections of the respiratory and gastrointestinal tract, these patients show increased susceptibility to autoimmune and allergic disorders including celiac disease, lupus, rheumatoid arthritis, autoimmune endocrinopathies, chronic active hepatitis, ulcerative colitis, Crohn’s disease, and autoimmune haematologic disorders [16].

The anti-inflammatory action of serum mIgA has been enigmatic until the discovery of IgA Fc receptors. Fc receptors are defined by their specificity for the Fc fragment of immunoglobulin isotypes, and receptors for IgA are referred to as Fc α R [6]. Although they are not structurally

related, there are several types of IgA receptors. Three of them are considered *bona fide* Fc α R. The first one is designated Fc α RI (or CD89), and is a receptor specific for IgA, capable of binding both human IgA1 and IgA2 subclasses. The additional Fc α Rs are the polymeric Ig receptor (PIgR), involved in Ig transport across epithelial barriers, and the Fc α / μ R, both having the common property of binding IgA and IgM. The four alternative IgA receptors are the asialoglycoprotein receptor, the transferrin receptor, FcRL4 and DCSIGN/SIGNR1 [6, 17].

Among these IgA receptors, the CD89 plays an essential anti-inflammatory role in immunity allowing transmission of inhibitory signals following binding of serum mIgA. CD89 is the only IgA Fc receptor expressed on blood myeloid cells including monocytes/macrophages, dendritic cells, Kupffer cells, neutrophils and eosinophils [6]. Interestingly, as do IgA, CD89 differs substantially between species since mice fail to express a CD89 homolog. CD89 can bind IgA1 and IgA2 with moderate affinity ($K_a \sim 10^6 \text{ M}^{-1}$) in the boundaries of CH α 2 and CH α 3 domains. While pIgA and IgA immune complexes (IC) bind with a greater avidity [18], mIgA binding to CD89 was found to be transient *in vitro* using surface plasmon resonance approaches. It seems reasonable, however, to assume that in the presence of high concentrations of circulating mIgA ($\sim 2 \text{ mg/ml}$), CD89 may be constantly occupied. Supporting this statement, there are indeed some evidences in the literature that IgA can be detected on the surface of monocytes and neutrophils, which was initially described as “cytophilic” IgA [19, 20]. Recently, we demonstrated for the first time that monovalent targeting of CD89 either by mIgA or by anti-CD89 Fab inhibits IgG-mediated phagocytosis in human monocytes [21, 22], explaining previously described inhibitory functions of serum IgA [8–14]. More importantly, we have been able to show that CD89-mediated inhibition was not associated with conventional inhibitory motifs such as the immunoreceptor tyrosine-based inhibition motif (ITIM). Indeed CD89 does not contain any ITIM in its cytoplasmic tail, but it can be expressed with or without physical association to the FcR γ adaptor [23]. While γ -less CD89 recycles monomeric IgA playing an essential role in mIgA homeostasis, FcR γ -associated CD89 mediates either activating or inhibitory responses [21] defining this receptor as a dual function receptor which operates depending on the type of the ligand: multimers or monomers. Both opposite functions were mediated by the FcR γ adaptor which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic tail. These data might explain why CD89 has been found as a unique member of the FcR family. Analysis of CD89 three dimensional structure reveals that it binds IgA in a manner different from other Ig isotypes. Its two Ig-like domains are oriented at right angles and two CD89 molecules can bind one IgA molecule within the EC1 domain, at a site completely different from the other FcRs, yielding a 2:1 stoichiometry as compared to the 1:1 stoichiometry of IgE and IgG to their FcRs [24]. The CD89 gene is not located in the FcR gene cluster but in chromosome 19, inside the leukocyte receptor cluster (LRC). CD89 is distantly related to other FcRs, being more homologous to LRC-encoded activating and inhibitory receptors [25].

Taken together, our findings on the functional regulation of CD89 allow the definition of a new inhibitory motif: the inhibitory ITAM or ITAMi [26]. ITAMi signaling results from an inhibitory configuration of the ITAM present within an activating receptor [26]. These configurations (activating vs inhibitory) are dependent on the way the ITAM-containing receptor interacts with its ligand. In the case of CD89, while highly multimeric interaction induces an activating signal, interactions of the receptor with ligands binding at low valency such as mIgA or anti-CD89 Fab fragments produce an inhibitory response. Indeed, the 2:1 stoichiometry of CD89: mIgA interaction can lead to receptor dimerization. This dimeric interaction generates an inhibitory signal, in contrast to the signal induced by multimeric receptor aggregation. The inhibitory signal is also generated with anti-CD89 Fab fragments, which in principle should target the receptor in a monomeric fashion.

Specific targeting of the ITAM-containing receptor with a weakly binding ligand (low affinity, low avidity, low valency) induces only scant ITAM phosphorylation thereby favoring the recruitment of signaling effectors such as the phosphatase SHP-1 with inhibitory potential [21, 27]. This is in contrast to highly multimeric ligation, which leads to a strong src-kinase mediated phosphorylation of FcR γ and recruitment of syk [28, 29]. Monovalent targeting of CD89 by Fab anti-CD89 or by mIgA prevented asthma, nephritis or inflammatory arthritis development in CD89 Tg mice [21, 22, 27].

Role of IgA receptors as pathogenic actors in IgA nephropathy

IgAN is the most common IgA-associated disease. The cause of IgAN, which is variable in the severity of its presentation, remains unknown. It occurs as a primary disease but it can be associated with Henoch Schönlein Purpura, celiac disease or inflammatory bowel disease. In IgAN, IgA deposited in the kidney are primarily pIgA1 [30]. There are many reports indicating that circulating IgA in patients with the disease are abnormal in terms of concentrations, molecular size or aggregation state. However, IgA concentrations may not be an essential pathogenic factor since in IgA myeloma patients, IgA deposition in the kidney are not correlated to serum IgA levels, indicating that there is a particularity in the composition of nephritogenic IgA1 complexes in IgAN. Moreover, increased serum levels of IgA are often found in other IgA-associated diseases such as Henoch-Schönlein purpura, ankylosing spondylitis, Sjögren's syndrome, alcoholic liver cirrhosis, celiac disease, inflammatory bowel disease, and dermatitis herpetiformis [31, 32]. Interestingly, a study has shown that the Fc α fragments of serum dimeric and trimeric but not mIgA1 aggregated to form multimers resistant to disruption in sodium-dodecyl-sulfate [33]. This might explain the propensity of pIgA to aggregate facilitating interaction with their receptors at leukocyte and tissue levels. There are also evidences that mesangial IgA1 exhibit a negative net charge [30] and decreased glycosylation [34] in IgAN, suggesting that this abnormal structural feature could underlie its pathogenic potential. The O-linked carbohydrate chains present in the hinge region of IgA1 in IgAN patients appear to be different from the one in normal individuals [35]. This lack of specific galactose residues could have marked effects on the properties of the molecule and create new epitopes that in turn could generate immune response with IgG antibodies against hypogalactosylated (Gd) IgA1 [36, 37]. The trigger for this abnormality is not known, but recent studies have shown that IgG anti-Gd-IgA1 antibodies are good markers of progression or recurrence after renal transplantation [38]. In addition, altered glycosylation favors self-aggregation of IgA1 [39].

Increased levels of IgA, are associated with aberrantly decreased expression of CD89 [20, 40–42]. Studies in IgAN patients, and patients with other IgA-associated diseases including HIV infection, alcoholic liver cirrhosis, and spondyloarthropathies, indicate reduced CD89 expression levels on circulating monocytes and, to a lesser degree, on neutrophils [20, 40–42]. Addition of IgA has a negative effect on CD89 expression [20], possibly due to shedding of CD89 extracellular domain [43] (**Fig.1A**). Indeed, production of soluble CD89 was induced *in vitro* by pIgA incubated with CD89-transfected cells. The demonstration of soluble CD89 in serum of IgAN patients and not in serum from healthy controls supports this hypothesis [44]. However, in contrast with the increased circulating levels of IgA1-IgG complexes observed in severe IgAN patients, levels of IgA-sCD89 complexes were decreased in these patients (or transplanted patients with recurrence of IgA1 deposits) suggesting that CD89-containing complexes could be selectively trapped in the mesangium aggravating the disease [45].

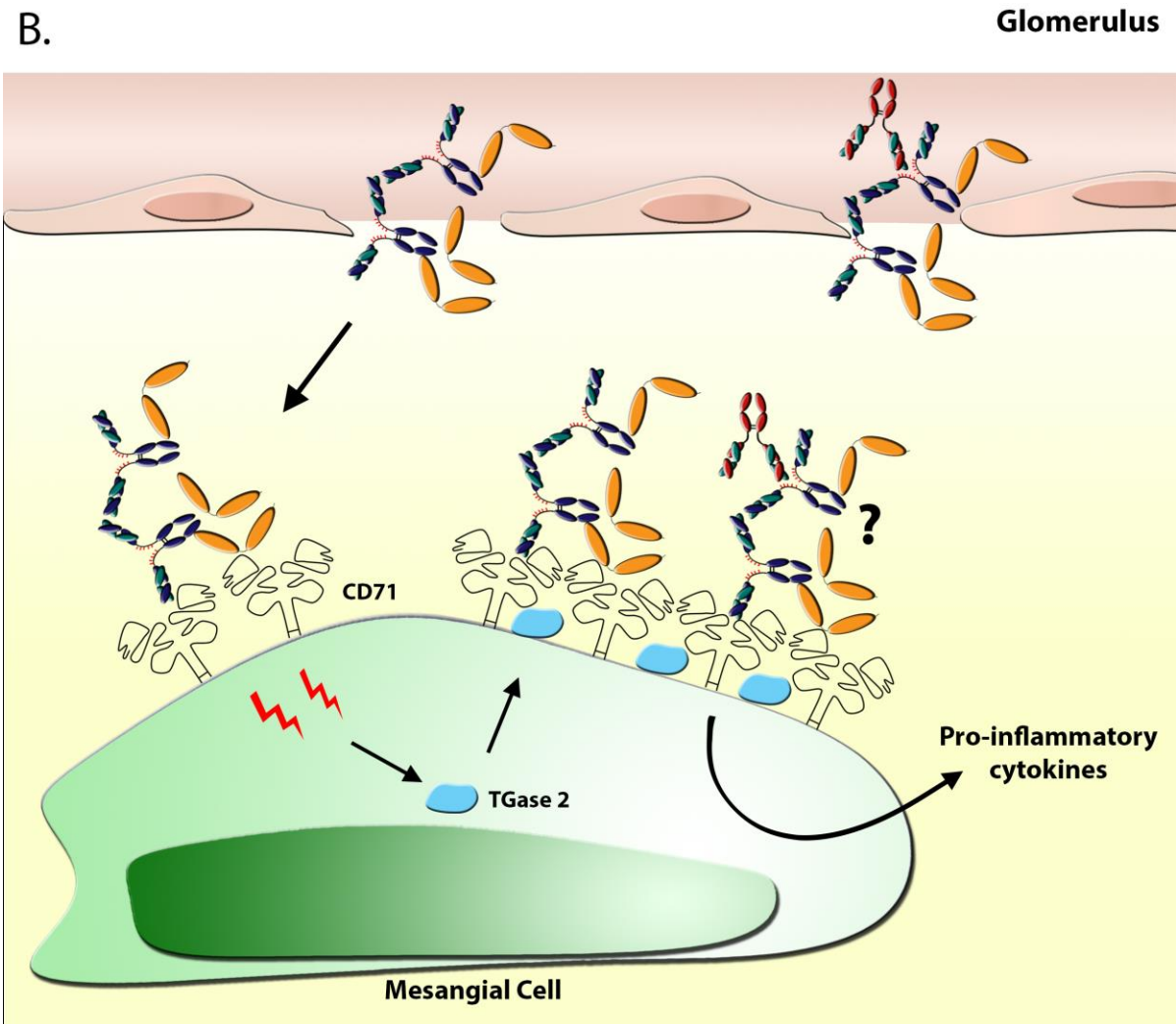
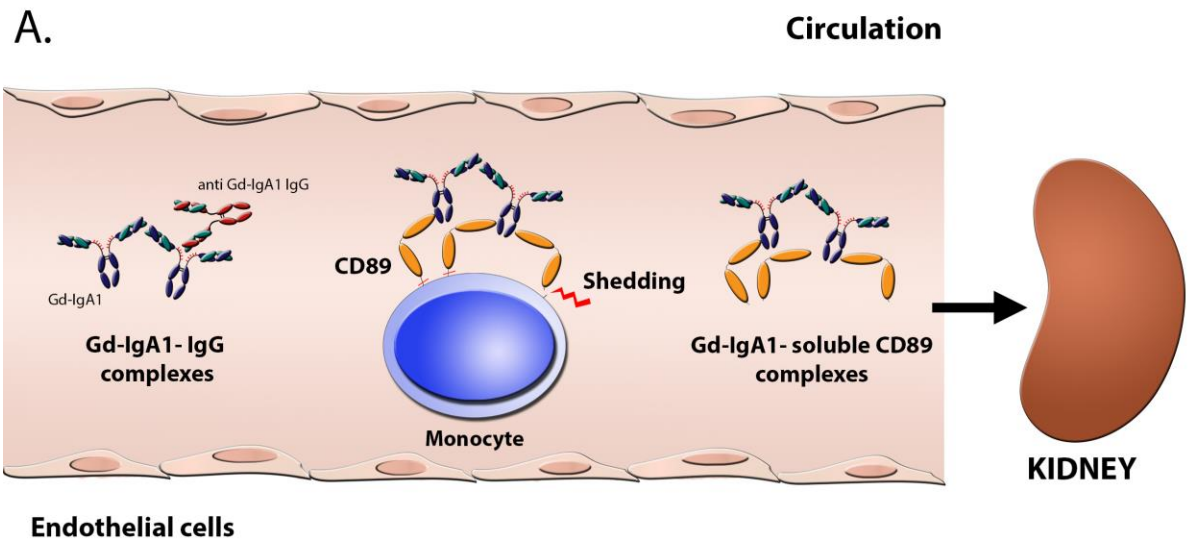
CD89 transgenic mice, in which the transgene is driven by a myeloid-specific promoter (human CD11b) conferring high CD89 expression on monocytes/macrophages, have been shown to spontaneously develop IgA nephropathy [43]. The mechanism in this model was shown to involve binding of mouse IgA dimers to human CD89 with subsequent receptor shedding and release of soluble CD89: IgA complexes that deposit in the kidney. However, these animals only developed mouse IgA deposits after 24 weeks of age due to the low affinity

between mouse IgA and human CD89 and failed to have renal function alterations. The pathogenic role of sCD89 was recently demonstrated using a double transgenic mouse model expressing both human CD89 and human IgA1 (α 1KI-CD89Tg mice) [46]. Circulating IgA1-sCD89 complexes in these mice were shown to induce mesangial deposits, hematuria and proteinuria compared to mice expressing human IgA1 alone. Moreover, sCD89 was detected in mesangial deposits in biopsies of patients with IgAN. This model also revealed that pathogenesis involves at least four elements; the interaction of IgA1-sCD89 complexes with another IgA1 receptor, the transferrin receptor 1 (CD71) and with the transglutaminase 2 (TGase 2), a cross-linking enzyme that may play a role in amplification of *in situ* pathogenic complex deposition in the mesangium.

The mechanism responsible for deposition of IgA1 complexes in the mesangium in IgAN has been indeed enigmatic for several years as patient mesangial cells fail to express CD89, Fc α / μ R, ASGP-R and poly-IgR [47] until the identification of the CD71 as a mesangial IgA1 receptor in patients with IgAN [48]. It has been demonstrated that IgA1 complexes and hypogalactosylated IgA1 have a higher affinity for CD71 and trigger inflammation, *via* the release from mesangial cells of pro-inflammatory cytokines (such as IL-1, IL-6 and TNF- α), and mesangial cell proliferation, with the potential to promote mesangial expansion and chemotactic activity towards leukocytes [49, 50]. Moreover, CD71 overexpression was associated with *in situ* ERK phosphorylation in biopsies of patients with severe disease [51]. However, lessons from transgenic animal studies suggest that *in situ* crosslinking of mesangial CD71 by both IgA and sCD89 in glomeruli is a necessary event. Soluble CD89 can bind CD71 and induce TGase 2 which in turn is translocated to the mesangial plasma membrane and allowing cell activation by IgA1-sCD89 complexes. Thus, CD89 and CD71 may cooperate with abnormal IgA1 to account for initiation, progression and chronicity of the disease (**Fig.1B**).

Figure 1: Proposed molecular mechanism involving IgA receptors in IgA nephropathy. A.

The pathogenic IgA1 complexes containing polymeric hypogalactosylated IgA1 (Gd-IgA1) alone or complexed with IgG anti-Gd-IgA1 antibodies may lead to enhanced IgA binding to CD89 on blood monocytes. This would generate soluble CD89/Gd-IgA1 complexes upon cleavage of FcR γ -less CD89. **B.** Soluble CD89/Gd-IgA1 (and/or eventually soluble CD89/Gd-IgA1-IgG) may get deposited in the mesangium through binding of IgA1 and sCD89 to CD71 receptor. This is a hypothetical representation as the two binding sites of these molecules to the CD71 remain unknown. The interaction of macromolecular IgA1 complexes with the CD71 receptor induces transglutaminase 2 expression at the mesangial cell surface which will lead into CD71 activation initiating an inflammatory feedback loop by inducing its enhanced expression together with cell proliferation as well as cytokine/chemokine production. The latter will further increase the inflammatory response and disease development.



Common IgA and IgA receptor dysfunctions in celiac disease (CD) and IgAN

IgA plays an important role in various inflammatory diseases, such as CD and IgAN. Two main questions are raised: a) Is there a correlation between these two diseases? b) How IgA is involved in this possible common pathogenic mechanism? Various studies have shown that IgAN occurs as a primary disease but it can be associated with Henoch Schönlein Purpura, CD or inflammatory bowel disease [52]. Indeed, the prevalence of CD in the general population is 0.5-1% depending on the geographical region and this percentage rises at 4% in patients with IgAN [53]. Inversely, CD may be a risk factor for renal disease, especially for IgAN. Glomerular mesangial deposits of IgA occur frequently in untreated CD and they are associated with circulating IC containing IgA [54]. However, in this situation IgA seems to be deposited without being able to induce clinically overt glomerulonephritis.

Coppo et al. have shown the presence of IgA anti-gliadin antibodies, associated with elevated IgA levels, in the serum of IgAN patients [55]. Moreover, IgA and IgG anti-endomysium antibodies were detected in the serum of IgAN patients [56]. These data suggest that dietary components (e.g. gliadin) may play a role in IgAN by promoting IgA IC formation and perhaps favoring mesangial localization *via* lectinic interactions, thus they propose a possible association between IgAN and CD [57]. This is supported by the finding that treatment with gluten free diet in IgAN patients [58] and animal models [55], decreased IgA IC and IgA anti-gliadin antibody levels in the serum, and ameliorated clinical symptoms of the disease, such as proteinuria and hematuria. However, in any case there was relentless progression to renal failure.

Concerning the mucosal immunity in IgAN, Kovács et al. have observed that IgAN patients compared to controls presented significantly higher intestinal permeability, related to increased proteinuria, microhematuria and serum IgA levels [59]. Thus, elevated intestinal permeability in IgAN patients may play a role in the pathogenesis of the disease and adversely influence its progression. Another study demonstrated the presence of a rectal mucosal sensitivity to gluten in one third of IgAN patients, but without any signs of CD, suggesting that such sub-clinical inflammation to gluten might be involved in the pathogenesis of IgAN in a subgroup of patients [60].

The pathogenic mechanism that links IgAN and CD is not yet clear [61]. It is known that lectins, particularly gliadins, can bind pIgA1 containing Gal and GalNac residues [57]. This reaction leads to the formation of macromolecular IgA1 IC. Interestingly, patients with CD display increased levels of Gd-IgA1 in the circulation [62]. Moreover, gliadin can also bind mesangial cells *via* lectinic bonds favoring the bridging of pIgA1 and IgA1 IC to these cells, and thus, enhancing both IgA1 mesangial trapping and *in situ* IgA1 deposit formation. Moreover, gliadin binding on mesangial cells modulates the production of immunological mediators and hemodynamic factors (increase of TNF- α and inhibition of prostaglandin E2 production) [57]. These changes might stimulate mesangial cell growth and mesangial matrix production, contributing to IgAN pathogenesis. Recent data from our laboratory has shown that gliadin can bind CD89 and induce nephrogenic sCD89-IgA1 complexes in α 1KI-CD89Tg mice [63]. Mice were rendered gluten sensitive by being submitted to a gluten-free diet for at least three generations. This led to a reduction in IgA1 mesangial deposition, a reduction in mesangial CD71 and TGase 2, reduced glomerular inflammatory-cell infiltration (CD11b+ and CD3+ cells), a reduction in hematuria, and reduced IgA1-sCD89 complexes in the serum and kidney eluates. Exposure to gluten in these sensitized mice led to intestinal injury, demonstrated by inflammation and villous atrophy, increased circulating IgA1-sCD89 complexes, mesangial IgA1 deposition, and elevated serum IgA1 anti-gliadin antibodies, that correlated with the level of proteinuria. Interestingly, a correlation was also found between anti-gliadin antibody levels in IgAN patients and proteinuria. Pertinently, early introduction of a gluten-free diet in α 1KI-CD89Tg mice at 3 weeks of age prevented the typical development of mesangial IgA1 deposition and hematuria [63]. This work provides novel mechanistic insights into the interactions required for IgA deposition and opens perspectives on further examination of the link

between IgAN, gliadin and IgA1-sCD89 complexes in large cohorts of IgAN patients with unexplained gastrointestinal symptoms.

The possible role of oral tolerance breakdown in the pathophysiology of IgAN has been already proposed, however there is still no clear evidence for the triggering factor of this process. It seems that the breakdown of oral tolerance can be favored by perturbations of epithelial cell function, resulting in abnormal processing of dietary antigens, such as gliadin, which renders them immunogenic rather than tolerogenic. In this case, the cytokines produced by the immune system activation influence the epithelial cell secretory component and class II antigen presentation. These modifications lead to intestinal permeability changes, allowing increased antigen uptake and presentation with stimulation of the mucosa immune system, resulting in mucosal inflammatory diseases, like CD. Furthermore, we have previously shown that in CD patients, the gliadin peptide 31-49 crosses the intestinal barrier without being degraded by the lysosomal pathway, using a mechanism similar in several aspects to those observed in IgAN (overexpression of CD71 at the apical surface of enterocytes) [64]. To conclude, the efficacy of gluten-free diet, together with the observed increase in intestinal permeability and in serum IgA reactivity to gliadin, and the increased levels of salivary and serum secretory IgA, have raised the assumption that the mucosal immune system plays an important role in IgAN physiopathology.

Conclusions

IgA-IgA receptor interactions play a significant role in the physiopathology of IgAN. The understanding of the molecular events involved in the pathological process will help to identify new partners that will be essential to generate new tools to treat this disease.

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