The Glomerular Response
to IgA Deposition in IgA Nephropathy

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Summary: Compelling evidence points to a role for IgA receptors in the pathogenesis of IgA nephropathy. The soluble form of the type I IgA receptor (FcαRI or CD89) forms complexes with IgA that can be found in patients' serum and that initiate the disease in CD89 transgenic mice. A nonclassic IgA receptor, identified as the transferrin receptor (TfR), is highly expressed in patients' mesangium and colocalizes with IgA deposits. TfR preferentially binds polymeric IgA1 complexes, but not monomeric IgA1 or IgA2. The TfR-IgA1 interaction is dependent on carbohydrate moieties because hypoglycosylated IgA1 has superior binding to TfR than normally glycosylated IgA1. Polymeric IgA1 binding enhances mesangial cell TfR expression and results in cell proliferation and inflammatory and profibrogenic cytokine and chemokine production, suggesting a pivotal role in mesangial cell proliferation, matrix expansion, and recruitment of inflammatory cells. We propose that, as a second event, activation of the classic, FcRγ-associated transmembrane FcαRI expressed on circulating myeloid leukocytes takes place. FcαRI/γ2 cross-linking in human FcαRI transgenic animals promotes disease progression by enhancing leukocyte chemotaxis and cytokine production, and IgA immune complexes from IgA nephropathy patients induce FcαRI-dependent cell activation. This review therefore details the functional consequences of IgA/receptor inter-actions and discusses proposed mechanisms to explain the development and chronicity of the disease.
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IgA deposition in the mesangium is the hall-mark of IgA nephropathy (IgAN). Early studies examined the type of IgA deposited as well as its physicochemical properties. It was found that mesangial IgA was of the IgA1 sub-class and contained predominantly, but not ex-clusively, λ light chains.[1,2] In some cases, IgA2 also has been identified in renal biopsy speci-mens.[3] Application of acid-elution techniques from renal biopsy specimens indicate that mes-angial IgA consists mainly of macromolecular IgA and IgA complexes.[4,5] These studies also suggest that mesangial IgA predominantly is an-ionic, consistent with abnormal glycosylation of the deposited IgA.[5] More recent studies[6,7] have shown alterations in the *O*-glycosylation of eluted IgA1 molecules, suggesting such glyco-forms of IgA1 are more likely to deposit in the kidney. Underglycosylation of IgA may lead to self-aggregation and formation of IgA1-IgA1 and IgA1-IgG immune complexes.[8,9] Interestingly, it recently was shown that dimers and polymers of IgA aggregate more readily than mono-mers,[10] which might explain the propensity for macromolecular IgA to aggregate and deposit in tissues. A number of investigators have sug-gested that an altered IgA immune response to specific antigens is responsible for the forma-tion of nephritogenic IgA antibody complexes in IgAN. Although it is possible that specific antigens may contribute to the formation of macromolecular IgA, there is no direct evi-dence to support this hypothesis.[11] IgA is

thought of principally as an anti-inflammatory immunoglobulin under physiologic conditions, present predominantly as a monomer in the serum where it interacts with IgA receptors on circulating blood cells.[12,13] The formation of aberrant IgA immune complexes in IgAN may importantly contribute to the inappropriate activation of circulating IgA receptor–bearing cells and resident glomerular cells. In this review we discuss the compelling evidence for the pathologic contribution of IgA/receptor interactions in IgAN.

IgA COMPLEXES IN THE INITIATION OF THE DISEASE

Besides the structural alterations of IgA described earlier, IgAN is characterized by the presence of high levels of IgA immune complexes both in the circulation and within mesangial IgA deposits.[11,14] IgA immune complexes are thought to develop by at least 3 distinct mechanisms: (1) self-aggregation of aberrantly glycosylated IgA1; (2) formation of complexes with soluble IgA Fc receptor I (FcαRI), and (3) interaction of IgA with other circulating proteins. The first of these mechanism is linked directly to the abnormal structure of IgA1 (reviewed by Novak, pp. 78-87).

The second mechanism relies on the binding of IgA with myeloid cell–expressed FcαRI (CD89), which through its α chain binds monomeric IgA of both IgA subclasses with low affinity, whereas multimeric IgA binds with high avidity.[15] In IgAN, soluble FcαRI can be detected in the serum and the presence of plasma IgA seems essential for this appearance. This was first shown by incubating myeloid cells from patients with IgAN with and without homologous plasma, and by incubating purified polymeric IgA (pIgA) with monocytes from normal individuals.[16] The mechanism proposed to explain this phenomenon involves shedding of the extracellular domain of the FcαRI.[14] Studies with metabolically labeled cells revealed the presence of a glycosylated soluble 50- to 70-kd form of FcαRI with a 24-kd protein core.[17] Production of soluble FcαRI is induced by polymeric IgA from FcαRI-transfected cells. These data indicate that cleavage of the FcαRI extracellular domain may occur, resulting in release

of IgA/FcαRI complexes into circulation. The shedding process involves FcαRI that are not associated with FcRγ.[17] Two other types of soluble FcαRI also have been described, which are released from eosinophils, neutrophils, and monocytes,[18,19] and differ from the 50- to 70-kd product. The eosinophil-/neutrophil-derived soluble receptor is a secreted splice product.[18] Interestingly, the monocyte-derived soluble FcαRI is a glycosylated 30-kd protein with a 25-kd backbone that is associated covalently with polymeric IgA.[19,20] It circulates in serum of normal individuals but is not increased in IgAN patients.[21] In contrast with the 50- to 70-kd soluble receptor, the shedding process of this 30-kd FcαRI is FcRγ dependent.[19]

The detection of circulating complexes containing IgA and the 50- to 70-kd form of soluble FcαRI in IgAN patients serum raise the possibility that these complexes may be involved in the development of this disease. To show this we generated human FcαRI transgenic mice, which serve as a novel animal model of spontaneous IgAN.[17] In this model, transgenically expressed human FcαRI binds mouse polymeric IgA, albeit with very low affinity, to form complexes that subsequently are deposited in the mesangium of the FcαRI transgenic mice. Human FcαRI transgenic mice develop mesangial IgA deposition, hematuria, mild proteinuria, and macrophage infiltration around the renal glomeruli.[17] The disease can be transferred to wild-type recipients by infusion of serum IgA/soluble FcαRI complexes from these transgenic mice. Recently, we also showed that transgenic mice expressing a mutated FcαRI$_{R209L}$ that is unable to associate with the FcRγ adaptor also have circulating soluble human FcαRI/mouse IgA complexes and develop IgA deposits and hematuria,[22] suggesting that the soluble, rather than the signal-competent, FcαRI is important for the onset of the disease. Nevertheless, others have failed to induce IgAN in mice after injection of recombinant soluble FcαRI fused to Fc fragment.[23] This failure could be the result of the short half-life of soluble FcαRI in transgenic mice. To examine the contribution of patient IgA, a model of severe combined immunodeficient (SCID)-FcαRI transgenic mice was created. Although these mice do not develop

IgAN spontaneously, they develop the manifestations of IgAN when IgA from IgAN patients are injected.[17] Interestingly, IgA from healthy subjects does not induce IgAN in these mice, implying that aberrant IgA together with FcαRI participate in the pathogenesis of IgAN.

The third mechanism for formation of IgA complexes in IgAN may involve IgA binding to other circulating proteins such as fibronectin, collagen, and laminin.[24-27] This also raises the possibility of an additional mechanism by which these IgA complexes might bind to the mesangium, not through IgA receptors but through adhesion to extracellular matrix proteins. In favor of this hypothesis, when uteroglobin, a serum protein that controls circulating fibronectin levels, is knocked out in transgenic mice these mice go on to develop IgAN.[28] However, no alterations of uteroglobin have been found in human IgAN.[29] Deposition of mannan-binding lectin (MBL) and MBL-associated serine protease in association with IgA in the mesangial area of patients with IgAN also have been reported.[30,31] Because IgA is glycosylated aberrantly in IgAN it also is possible that IgA binding to MBL and MBL-associated serine protease may contribute to the formation of IgA complexes in IgAN.

ACTIVATION OF MESANGIAL CELLS BY ABERRANT COMPLEXED IgA

Mesangial cell proliferation and matrix expansion are characteristic features of IgAN. This process seems to be dependent on IgA-induced triggering of mesangial cell activation. Several studies have shown that IgA complexes are capable of inducing human mesangial cell (HMC) activation. Binding of IgA1 complexes induces an increase in intracellular Ca^{2+}, PLC-γ1 activation, production of inositol trisphosphate, and protein tyrosine phosphorylation.[32] As a consequence, mesangial cells release cytokines such as interleukin (IL)-6, IL-8, and IL-1β, but also profibrogenic transforming growth factor-β.[33-35] They also proliferate and synthesize extracellular matrix proteins. Furthermore, it has been shown that abnormally glycosylated IgA is able to modulate human mesangial integrin expression and vascular endothelial growth factor synthesis.[36] These results point to the existence of a mes-

angial IgA receptor that could link IgA and HMC activation.

MESANGIAL IgA RECEPTORS

It has been postulated that HMCs express a number of different IgA receptors. Many investigators have studied direct interactions of serum IgA with mesangial cells and matrix components. A number of IgA receptors have been identified on different cell types: the hepatic asialoglycoprotein receptor, the myeloid FcαRI/CD89 receptor, the mucosal polymeric Ig receptor, the B cell and macrophage Fcα/μR, and the transferrin receptor (TfR).[37-41] Studies from several groups have now excluded the asialoglycoprotein receptor, FcαRI/CD89, and the pIgR as being mesangial cell IgA receptors.[34,42-45] Although mesangial cells express messenger RNA for Fcα/μR,[46] IgA1 binding to mesangial cells was not inhibited by IgM[43] or by recombinant Fcα/μR,[47] and no expression of the Fcα/μR protein by HMC has been reported, indicating a modest role for this receptor in the glomerulus. By contrast, there is overexpression of TfR in the mesangium of patients with IgAN and Henoch-Schönlein purpura.[48] Interestingly, this TfR overexpression is colocalized with IgA deposits, indicating that TfR may be a mesangial IgA receptor involved in the formation of IgA1 deposits. Furthermore, TfR overexpression by mesangial cells also has been observed in patients with lupus nephritis with IgA deposits, but not in those with no such deposits.[48] Expression of TfR messenger RNA (CD71) by proliferating mesangial cells was confirmed recently.[42] TfR binds pIgA1 and has a higher avidity for underglycosylated IgA1 and for IgA1 complexes than for normal IgA1.[47] Several investigators agree that the Fc portion of the IgA1 molecule mediates binding of IgA1 to mesangial cells because both intact IgA1 and the Fc portion, but not its Fab fragment, inhibit binding of IgA1 to mesangial cells.[42,43,47] We have shown that IgA1 binding to TfR is likely to be mediated by the IgA1 hinge region and involve the associated carbohydrate moieties.[47] By using a variety of mutated recombinant dimeric IgA1 molecules we observed that deletion of either *N*- or *O*-linked glycosylation sites abrogated IgA1 binding to TfR, suggesting that sugars are essential for IgA1 binding. However, sialidase and

β-galactosidase treatment of IgA1 significantly enhanced IgA1/TfR interaction. These results indicate that aberrant glycosylation of IgA1 as well as immune complex formation constitute essential factors favoring mesangial TfR-IgA1 interaction during the initial phase of IgAN pathogenesis. We recently showed that macromolecular IgA1 is a major inducer of TfR expression (3- to 4-fold increase) in quiescent HMCs.[35] IgA-induced, but not cytokine-induced, HMC proliferation was dependent on TfR engagement because proliferation was inhibited by both TfR1 and TfR2 ectodomains as well as by an anti-TfR monoclonal antibody A24. It is noteworthy that TfR up-regulation is dependent on the continued presence of IgA1 rather than on soluble factors released during IgA1-mediated activation. In addition, pIgA1 induced IL-6 and transforming growth factor-β production from HMCs was inhibited specifically by the monoclonal antibody A24, confirming that pIgA1 triggers TfR-dependent HMC activation. In this study, up-regulation of TfR expression induced by sera from patients with IgAN, but not from healthy individuals, was dependent on IgA.[35] We propose that deposited pIgA1 or IgA1 immune complexes initiate a process of auto-amplification involving overexpression of TfR by HMCs promoting increased IgA1 mesangial deposition. These data suggest a functional cooperation between pIgA1 and TfR in the mechanisms of IgA1 deposition and HMC proliferation and activation. These mesangial changes are implicated commonly in the development of ongoing glomerular injury in IgAN and also may explain the recurrence of IgA1 deposits in the mesangium after renal transplantation (Fig. 1). Finally, there is some evidence for the expression of other IgA receptors in the mesangium, but currently they remain unidentified.[42,43]

MESANGIAL IgA COMPLEXES ACTIVATE THE MYELOID FCαRI AND MEDIATE DISEASE PROGRESSION

Clinical observations studying progression of IgAN associated with mononuclear cell infiltration in the kidney suggest that leukocytes may play a role in glomerular damage and interstitial tissue injury.[49,50] Experimental evidence for the implication of the classic myeloid IgA receptor,

Figure 1. Pathophysiologic circuits in the development of mesangial injury initiated by the interaction of IgA1-IC with a mesangial IgA receptor, the TfR. Interaction of macromolecular IgA complexes with the TfR initiates an inflammatory feedback loop by inducing enhanced TfR expression and mesangial cell proliferation as well as cytokine/chemokine production. The latter further increase the inflammatory response and development of fibrosis by influencing other cell types that promote ongoing inflammation. Whether the mesangial cell proliferation is a direct result of IgA-TfR interaction or occurs secondary to cytokine production by activated mesangial cells still is unresolved (dotted arrows).

namely FcαRI, in glomerular infiltrating leukocytes in IgAN come from studies by Kashem et al.[51] These investigators detected FcαRI messenger RNA in patient's glomeruli and their damaged tissues.[51] Additional observations have indicated that in IgAN leukocytes have large amounts of IgA bound to transmembrane FcαRI[16,52] and that the level of receptor occupancy correlates with the presence of glomerulosclerosis.[16]

Recently, we provided evidence that multimeric aggregation of FcαRI induces an inflammatory response with priming and cytokine/chemokine release that is an integral component of IgAN pathogenesis mediating disease progression.[22] Previous studies have indicated that the FcαRI α chain partly associates with the common FcRγ chain, which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. The FcαRI-FcRγ interaction has a dual function because it can mediate either cell

activation after multimeric aggregation of the receptor or inhibition after interaction with monomeric ligand.[13] Although in health the interaction between serum IgA and FcαRI favors an anti-inflammatory outcome,[12,13] in disease this balance is tipped toward an inflammatory response. This may be relevant in IgAN, in which one observes the presence of circulating IgA-IC, which when bound to myeloid FcαRI could trigger inflammatory signaling.[16,52]

The importance of this FcαRI-FcRγ interaction in the promotion of inflammatory damage was revealed through analysis of the differences in disease development in transgenic mice expressing either wild-type FcRγ-associated or mutant FcRγ-less FcαRI. Although both transgenic mice spontaneously develop mesangial IgA deposits and hematuria (see earlier), only animals expressing wild-type FcαRI that can associate with FcRγ develop proteinuria and macrophage accumulation in the glomeruli and periglomerular space.[22] Furthermore, only macrophages carrying wild-type FcαRI, but not those carrying FcRγ-less FcαRI, were able to migrate to the kidney on adoptive transfer, clearly suggesting the dependency of this chemotaxis on the association of the receptor with FcRγ. Therefore, binding of pathologic IgA-IC and signaling through FcRγ results in priming of monocytes that together with mesangial
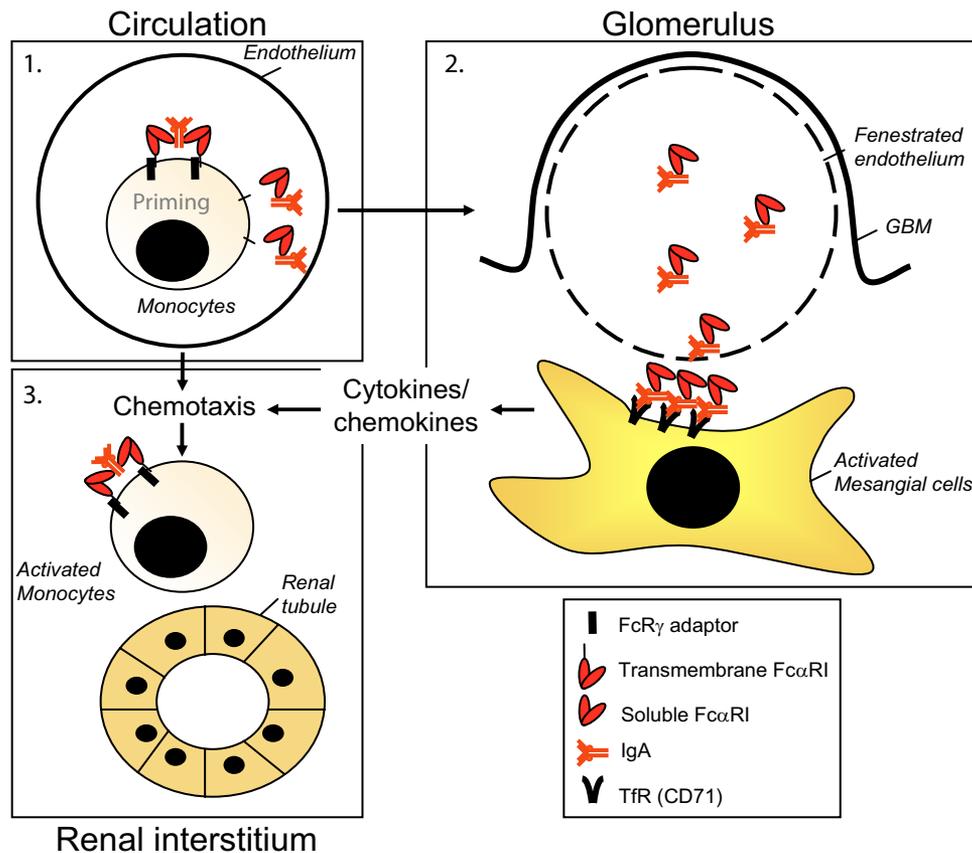
Figure 2. Proposed model for IgAN pathogenesis involving 2 IgA receptors. The essential steps are as follows. First, the generation of pathologic macromolecular IgA complexes results in enhanced IgA binding to blood monocytes in the circulation. This leads to the following: (1) cleavage of FcαRI molecules that are not associated with FcRγ and the generation of soluble FcαRI/IgA complexes, and (2) activation (priming) of circulating monocytes through cross-linking of transmembrane FcRγ-associated FcαRI. Second, soluble FcαRI/IgA molecules are deposited in the mesangium and binding of IgA1 to TfR initiates the production of inflammatory cytokines and chemokines. Third, mesangial cell–derived inflammatory mediators act on primed monocytes to promote inflammatory cell infiltration into the renal interstitium, thereby further amplifying the inflammatory process and promoting progression to end-stage renal disease.

cell–produced chemokines promotes the migration of leukocytes into the renal interstitium and periglomerular regions, thereby amplifying glomerular lesions through FcαRI/FcRγ$_2$ activation. Lessons from transgenic studies have suggested that in situ cross-linking of mesangial TfR by IgA-IC in glomeruli is an initial necessary event, but not sufficient to promote disease progression. This is summarized in Fig. 2.

Although wild-type FcαRI transgenic mice show increased macrophage infiltration they do not develop end-stage disease, suggesting that this model resembles patients with a mild disease course. This may be owing to the low-affinity binding of pIgA to FcαRI and consequent reduced cross-linking of FcαRI by macromolecular IgA or IgA complexes in the mouse. We have, however, been able to show the importance of continuous FcαRI cross-linking in the development of renal failure by using a murine model of severe glomerulonephritis induced by the injection of anti–glomerular basement membrane antibodies into wild-type FcαRI transgenic mice. In this model renal injury was worsened markedly in mice transgenic for FcαRI associated with FcRγ, but no worsening of the observed glomerulonephritis was seen in FcαRI$_{R209L}$ transgenic mice, highlighting the pathogenic role of FcRγ signaling in disease progression. Consistent with these observations, serum IgA-IC from patients with IgAN induced cell activation and inflammatory cytokine production, indicating that serum IgA can trigger inflammatory signaling through FcαRI in IgAN and that this is relevant for disease. Such inflammatory signaling may be enhanced further if patients express an increased proportion of signal-competent FcRγ-associated receptors.[22] Together with the results obtained in transgenic mice these data also may help explain the well-described heterogeneity in the natural history of IgAN because the potential for inflammatory signaling was different between patients.[22]

Finally, other non-IgA receptor–mediated, but IgA-dependent systems, also may contribute to progression of IgAN. It has been shown that the complement system can be activated by human IgA via both the alternative and the lectin pathways, which are driven mainly by MBL.[53] Activation of the lectin pathway in the renal mesangium is supported by deposition of MBL and MBL-associated serine protease in association with IgA in the mesangial area of patients with IgAN.[30] Recent data support a role for the lectin pathway of complement in local glomerular complement activation in IgAN and suggest that complement activation also may influence progression of the disease.[31] Therefore, it is likely that deposited pIgA contributes to the development of renal damage by both local activation of complement (reviewed by Oortwijn, pp. 58-65) and mesangial cell activation.

CONCLUDING REMARKS

Accumulated data in patients and animal models reveal that the pathogenesis of IgAN involves multiple factors that combine to generate a heterogenous picture of disease development. The essential events can be divided into 3 steps: (1) the generation of aberrant macromolecular IgA1 that promotes shedding of soluble FcαRI and priming of monocytes through signal-competent FcRγ-associated transmembrane FcαRI, (2) mesangial activation mediated by interaction of macromolecular IgA1 with mesangial IgA receptors, and (3) disease progression through the combined action of mesangial and leukocyte cell activation that may involve several inflammatory pathways.

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