Deposition of IgA in primary IgA nephropathy: it takes at least four to tango*

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ABSTRACT

Berthelot et al. investigated the role of different players in the induction of IgA-mediated inflammation combining mice with a knock-in of the human IgA1 heavy chain (α1KI), with mice expressing the human IgA receptor CD89 (CD89Tg). These experiments suggest that IgA1 interacts with CD89 on mononuclear cells and induces the release of sCD89 and the formation of IgA1–CD89 complexes. These complexes then interact with the transferrin receptor (CD71/TfR1) on mesangial cells and further enhance the expression of TfR1 via transglutaminase-2 (TGase2). TGase2 is a calcium-dependent enzyme that is involved in cross-linking proteins through the formation of ε(γ-glutamyl)-lysine bonds. TfR1 and TGase2 were both shown to bind sCD89, but also to directly interact with each other, providing an amplification step for IgA1 accumulation and inflammation in the kidney. Importantly, when α1KI/CD89 Tg mice were crossed with TGase2-deficient mice, both IgA deposition and renal disease were strongly attenuated. Immunohistochemical studies demonstrated the enhanced mesangial deposition of IgA1–sCD89 complexes not only in Tg mice, but also in biopsies of a limited number of patients with IgAN and not in controls. Taken together, these exciting and detailed studies reveal a number of results that are of importance for our understanding of the intricate mechanisms that may lead to the deposition of IgA1 in the mesangium and the minimum requirements for the induction of an inflammatory cascade leading to glomerular damage and decline of renal function.

SHORT REVIEW OF THE FIELD

IgAN is characterized by deposits of mainly IgA1 in the mesangium of glomeruli and is the most common form of primary glomerulonephritis worldwide [1, 2]. At least part of the deposited IgA in the kidney is in a J-chain containing the polymeric form, capable of binding secretory component ex vivo. Various studies have revealed that the IgA in the deposits is under-glycosylated [3–5]. The observation of the frequent recurrence of disease in renal allografts [6] suggests that the glomerular IgA is derived from the circulation and that molecular alterations might be intrinsic to the IgA molecules. The finding of increased serum levels of polymeric IgA restricted to the IgA1 subclass in patients with IgAN supports this concept. Initially it was shown that at least part of the origin of the polymeric IgA lies within the bone marrow [7]; however, there is also a clear link with the mucosal compartment, both clinically (‘synpharyngitic haematuria’) as well as through the demonstration of secretory SIgA in the mesangial deposits [8].

Much is known about the inflammatory capacity of polymeric IgA in vitro but little is known about the factors that determine the binding of IgA to mesangial cells or the mechanisms involved in the deposition of IgA from the circulation into the kidney. IgA receptors have been proposed to play a
role in this mesangial deposition of IgA, as well as in the activation of mesangial cells. The bona fide Fc receptor for IgA (FCγR1/CD89) has received attention as a potential mesangial IgA receptor. CD89 that is abundantly expressed on myeloid cells, including monocytes/macrophages and neutrophils, is associated with the common γ-chain and has a strong pro-inflammatory function [9]. However, CD89 has been detectable in neither kidney sections of normal or IgAN kidneys nor on cultured mesangial cells using monoclonal and polyclonal anti CD89 antibodies [10, 11].

An exciting new observation was made in mice with transgenic overexpression of human CD89 in monocytes/macrophages [12]. These mice spontaneously developed mesangial IgA deposition, glomerular and interstitial macrophage infiltration, mesangial matrix expansion, haematuria and mild proteinuria. The molecular mechanism was shown to involve soluble CD89 released after interaction of IgA with monocytic CD89 (Figure 1). The disease could also be induced in recombination activating gene (RAG)2(−/−) mice by injection of serum from Tg mice, and in severe combined immunodeficiency (SCID)-Tg mice by injection of the patient’s IgA. Depletion of soluble CD89 from serum abolished this effect. However, injection of recombinant soluble CD89 into naïve mice did not result in detectable IgA–sCD89 complexes in the kidney [13].

Subsequent studies revealed a role of the transferrin receptor (TfR1), a receptor that can be found on activated mesangial cells, and apart from it’s role in transferrin uptake, it also serves as a receptor for IgA or IgA–sCD89 complexes [14, 15]. Importantly, these studies also suggested that the glycosylation of the IgA1 will affect the complex formation with CD89. However, some of the findings in the mouse model were still difficult to reconcile with the observation that murine IgA has a very low affinity for human CD89 [13, 16]. Therefore, others proceeded to develop a transgenic mouse with a knock-in of the human IgA1 heavy chain [17]. These transgenic mice expressing human IgA1 do show renal IgA deposits, however, they only display endocapillary deposition of IgA1 without mesangial injury or kidney dysfunction.

The publication of Berthelot et al. now has brought a number of these observations together with the recent results of another player in the field of renal inflammation and fibrosis, namely transglutaminase-2 (TGase2) [21]. TGase2 (also known as TG2) is a calcium-dependent enzyme that is involved in cross-linking proteins through the formation of ε(γ-glutamyl)-lysine bonds [18]. Extracellular TGase2 has the capacity to irreversibly crosslink matrix proteins including collagens and proteoglycans. Moreover, TGase2 is able to activate TGF-β, thereby contributing to the process of fibrosis. Indeed, TGase2-deficient mice showed reduced interstitial fibrosis and cross-linked collagen in a model of unilateral urethral obstruction [19]. It was previously demonstrated that TGase2 staining in kidneys of patients with IgAN is correlated with serum creatinine, creatinine clearance, protein excretion, glomerulosclerosis and mesangial cell proliferation [20].

The studies of Berthelot et al. now demonstrate that TGase2 is also involved in a process of auto-amplification of IgA binding, initiated by binding of IgA1–sCD89 complexes to mesangial TfR1, followed by enhancement of expression of TfR1 [21]. This then results in increased binding of IgA1–sCD89 complexes, hyper-expression of TfR1 as well as

FIGURE 1: Schematic model of molecular interactions involved in the deposition of IgA1. IgA1 produced by B cells is partially underglycosylated and can interact with CD89 on myeloid cells. This interaction results in the release of a soluble CD89 molecule and sCD89–IgA1 complex formation. These complexes travel from circulation to the kidney and can interact with TfR1 on mesangial cells. This interaction increases TfR1 expression, but also induces TGase2. TGase2 is able to bind sCD89–IgA1 but also to directly interact with TfR1. All together this results in an amplification of binding as well as an increased production of inflammatory mediators.
induction of TGase2, which can also bind IgA1–sCD89 complexes. In addition, there is a direct interaction between TfR1 and TGase2, all together allowing increased deposition of pathogenic IgA1 complexes and chronic mesangial cell activation (Figure 1) [21]. When only patients with IgAN would display circulating IgA1–sCD89 complexes, this series of events could be an explanation for the development of IgAN. However, recently it has been reported that IgA–sCD89 complexes are not only found in patients with IgAN, but also in healthy controls [22]. These investigators found an association of soluble CD89 levels with disease progression but not susceptibility of IgA nephropathy. Therefore, one would be inclined to reason that additional controlling mechanisms must be operational to determine the balance of inflammation and injury in the human situation. There are at least two additional pathogenic factors, which have been demonstrated to play a role in either complex formation, mesangial deposition and/or glomerular inflammation: IgG antibodies reacting with the under-glycosylated hinge region of IgA1 [23, 24] and the capacity to induce local complement activation including the interaction of IgA with Mannan-binding lectin [25].

**WHAT DOES THIS MEAN FOR THE PRACTICING NEPHROLOGIST?**

For the time being, these findings will not affect clinical practice. There is much room for further investigation of the role of the mentioned molecular partners in human IgAN using a well-defined groups of patients and controls. Especially, the relationship between circulating and deposited IgA1–sCD89 complexes and disease severity requires attention. Additionally, the local protein expression of TfR1, TGase2, IgA1–sCD89 complexes in relation to clinical symptoms and severity of the renal lesions have to be analysed. Until now it had not been possible to demonstrate the presence of CD89 in glomerular deposits. This current study describes a new antibody which does have this capacity, so it will be important to expand these observations to larger patient cohort and for instance to relate this to the new pathology scores for IgAN [26].

The identification of a role of TGase2 might provide new therapeutic options, and in an experimental rodent model (5/6 nephrectomy) treatment with TGase inhibitors has already been demonstrated to prevent decline in renal function and to slow down glomerulosclerosis and tubulointerstitial fibrosis [27]. Once we know more details about these relationships in the human situation then one can decide on the most suitable approach to use the exciting findings presented in the publication of Berthelot et al. for potential interference with disease activity in IgAN.

**TAKE-HOME MESSAGE**

It seems that we have come closer to answering the million dollar question in IgAN, namely the elucidation of the mechanisms for initial deposition of IgA1 in the kidney. Deposition seems to be a multi-molecular process involving at least four different proteins. However, it is not unlikely that additional partners will join the party and there is still a way to go.

**CONFLICT OF INTEREST STATEMENT**

None declared. The results presented in this review have not been published previously in whole or in part.

**REFERENCES**

The relevance of dietary sodium in hemodialysis

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Since the earliest days of hemodialysis, dietary sodium restriction has been recommended as a therapeutic means to mitigate problems of extracellular volume overload, hypertension and inter-dialytic weight gain. Recently, there has been a proliferation of human subjects’ research examining the potential effects of dietary sodium curtailment. Herein we examine the available evidence with respect to the effects of dietary sodium restriction on clinically relevant endpoints among hemodialysis patients.

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