Reduced binding of immunoglobulin A (IgA) from patients with primary IgA nephropathy to the myeloid IgA Fc-receptor, CD89

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Abstract

Background. Primary IgA nephropathy (IgAN) is associated with elevated levels of circulating IgA and is characterized by deposition of primarily IgA1 in the renal mesangium. It has not yet been clarified which mechanisms govern the deposition of IgA1 in the mesangium. One of the factors which may play a role in trapping of IgA in the mesangial area is the interaction of IgA with specific IgA receptors (FcεR, CD89) on the mesangial cells.

Methods. In the present study IgA derived from patients with IgAN and controls was investigated for its interaction with human CD89, expressed on the surface of the murine B cell line IIA1.6.

Results. IgA binding to CD89 expressing cells was specific, concentration dependent and binding of dimeric IgA complexes in vivo, next to clearance via the asialoglycoprotein receptor, is thought to occur via IgA Fc receptor mediated phagocytosis. It has been found that the binding of IgA-immune complexes can activate macrophages and thus lead to the elimination of IgA-containing immune complexes. In patients with IgAN a defective clearance of IgA has been suggested. Other IgA mediated effector functions such as ADCC, superoxide generation, and release of cytokines and inflammatory mediators have been linked to tissue damage. These functions are regulated via binding of IgA to its cognate Fc receptor termed FcεRI or CD89. In addition, IgA can interfere with binding of di- and polymers of IgA, CD89 could still contribute to IgA deposition in the mesangial area.

Conclusions. The reduced binding of IgA to CD89 seems to contradict a direct role for CD89 in deposition of IgA. However reduced binding of IgA to CD89 may affect IgA clearance, leading to higher serum IgA. Furthermore, since it has been demonstrated that IgA can interfere with binding of dimeric IgA, CD89 could still contribute to IgA deposition in the mesangial area.

Key words: CD89; Fc receptor IgA; IgAN

Introduction

Primary IgA nephropathy (IgAN) is a common form of primary glomerulonephritis with a broad spectrum of clinical presentations, leading to progressive renal failure in a substantial proportion of patients. The disease is characterized by increased production of polymeric IgA1 by the bone marrow and by deposits of IgA1 in the glomerular mesangium. IgA has been found to consist at least in part of polymeric IgA (pIgA). The mechanisms responsible for the mesangial deposits remain unclear.

IgA1-containing immune complexes are thought to be of pathogenic importance in IgAN. An important elimination mechanism of IgA-containing immune complexes in vivo, next to clearance via the asialoglycoprotein receptor, is thought to occur via IgA Fc receptor mediated phagocytosis. It has been found that the binding of IgA-immune complexes can activate macrophages and thus lead to the elimination of IgA-containing immune complexes. In patients with IgAN a defective clearance of IgA has been suggested. Other IgA mediated effector functions such as ADCC, superoxide generation, and release of cytokines and inflammatory mediators have been linked to tissue damage. These functions are regulated via binding of IgA to its cognate Fc receptor termed FcεRI or CD89. In addition, IgA can interfere with binding of di- and polymers of IgA, CD89 could still contribute to IgA deposition in the mesangial area.

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characteristics of IgA from sera of patients with IgAN and controls to CD89. We found that monomeric IgA of patients with IgAN showed a diminished binding to CD89 compared to controls.

Subjects and methods

Patients

Serum samples were collected from 23 patients with IgAN (19 males, four females) mean age 36 years (range 19–59 years). All patients had clinically quiescent disease, with biopsy-proven IgAN, defined by mesangial deposits of IgA as the dominant isotype. Laboratory data of patients were: creatinine clearance > 80 ml/min; urinary protein < 2 g/24 h. As controls we used serum samples from 17 matched healthy volunteers. Neither patients, nor controls, had symptoms or signs of mucosal infection in the 2 weeks preceding the study.

Reagents

CD89 was detected by the mAb A77 (mouse IgG1), kindly provided by Dr R. C. Monteiro [12]. For inhibition experiments culture supernatants from clone MY43 (mouse IgM) were used [13], kindly provided by Dr Li Shen. A panel of mAbs with specificity for human IgA, IgA1 and IgA2 resp. clone 4E8, clone 69-11.4 and clone 16-512-H5 (all mouse IgG1) [14], were used for detection of human IgA. Mouse mAbs were either detected with PE-labelled goat-anti-mouse IgG1 polyclonal antiserum by flow cytometry (Southern Biotechnology, Birmingham, AL) or with HRP-labeled goat-anti-mouse IgG polyclonal antiserum by ELISA (Tago, Burlingame, CA).

Cell culture

The murine B-cell line IIA1.6 [15] was cultured in RPMI 1640 medium (Life Technologies, Breda, The Netherlands) supplemented with 10% heat-inactivated FCS (Life Technologies). IIA1.6 was transfected with CD89 cDNA and stable cell surface expression was maintained by cotransfection of human γ-chain cDNA, as described previously [15]. The CD89-transfectants were grown in the same medium supplemented with geneticin (G418, 0.8 mg/ml; Life Technologies) and methotrexate (MTX, 10 mmol/l; Pharmachemie, Haarlem, The Netherlands). The human monocytic like cell line, U937 was cultured in RPMI 1640 supplemented with 10% heat-inactivated FCS.

Detection of CD89

CD89-transfected and control cells were tested for CD89 expression by FACS analysis using CD89 mAb A77. Cells (5 × 10^5) were washed twice with FACS buffer (PBS/0.5%BSA) and incubated for 1h at 4°C with A77 culture supernatant diluted in FACS buffer. Following incubation, cells were washed twice (FACS buffer) and incubated for 1 h with a goat anti-mouse IgG1-PE polyclonal antiserum diluted in FACS buffer. After washing twice with FACS buffer, cells were fixed in 1% paraformaldehyde in PBS and analysed on a FACSScan (Becton Dickinson, San Jose, CA). Data acquisition and analysis were conducted with Lysis II (Becton Dickinson).

Purification of IgA

Human IgA from sera of multiple myeloma patients with IgA1 or IgA2 paraproteins was isolated by euglobulin, ZnSO₄ and (NH₄)₂SO₄ precipitation followed by DEAE Sephacryl (Pharmacia, Uppsala, Sweden) anion exchange chromatography, and Sephacryl S-300 (Pharmacia) gel filtration, as described previously [16]. The IgA preparations were shown to contain <0.1% of IgG or IgM by ELISA and were free of other protein contaminants as assessed by SDS–PAGE analysis under reducing conditions.

Binding and detection of purified IgA preparations to CD89-transfected IIA1.6 cells

CD89-transfected and control cells were tested for binding of purified IgA preparations, by FACS analysis. Cells were washed twice (FACS buffer) and incubated for 1h with varying concentrations of purified IgA preparations, diluted in FACS buffer. Following incubation, cells were washed and bound IgA was detected by incubation with a panel of mAbs with specificity for human IgA, IgA1 or IgA2 and subsequently with PE-labelled goat anti-mouse IgG1 polyclonal antiserum. The geometric Mean Fluorescence Intensity (MFI) was used as a measure for binding of IgA.

Inhibition of IgA binding to CD89-transfected IIA1.6 cells

To define the specificity of IgA binding to CD89, blocking studies were performed using CD89 mAb MY43. Briefly, MY43 culture supernatants from clone MY43 (mouse IgM) or clone 4E8, clone 69-11.4 and clone 16-512-H5 (all mouse IgG1) [14], were used for detection of human IgA. Mouse mAbs were either detected with PE-labelled goat-anti-mouse IgG1 polyclonal antiserum by flow cytometry (Southern Biotechnology, Birmingham, AL) or with HRP-labeled goat-anti-mouse IgG polyclonal antiserum by ELISA (Tago, Burlingame, CA).

Quantification of IgA in sera

Sera from patients with IgAN (n = 23) and controls (n = 17) were analysed for total IgA, IgA1 and IgA2 concentrations stable cell surface expression was maintained by cotransfection of human γ-chain cDNA, as described previously [15]. The CD89-transfectants were grown in the same medium supplemented with geneticin (G418, 0.8 mg/ml; Life Technologies) and methotrexate (MTX, 10 mmol/l; Pharmachemie, Haarlem, The Netherlands). The human monocytic like cell line, U937 was cultured in RPMI 1640 supplemented with 10% heat-inactivated FCS.

Fractionation of serum IgA

Randomly selected sera from patients with IgAN (n = 6) and controls (n = 6) were separated by size on a 1.5 × 90 cm Sephacryl S300 column. Briefly, 0.5 ml aliquots of sera were diluted with an equal volume of PBS layered on the column and fractions of 1.25 ml/6 min. were collected. The fractions were analysed for total IgA by ELISA and the binding of IgA to CD89-transfected IIA1.6 cells was tested as described above.

Binding of IgA (IgA1 and IgA2) directly from serum of patients and controls to CD89-transfected IIA1.6 cells

Binding of IgA directly from sera of patients with IgAN and controls was determined as follows: sera were diluted 1/50 in FACS buffer and added to nontransfected or CD89-transfected IIA1.6 cells. After incubation for 1h at 4°C, cells were analysed for total IgA, IgA1 and IgA2.
binding, with respectively mAb 4E8, 69-11.4, and 16-512-H5 as described above.

Statistical analysis

All statistical calculations were performed using SPSS (for windows, release 6.0 software package). The concentrations of IgA and IgA subclasses in sera of patients and controls were transformed logarithmically prior to analysis. Comparisons between groups were performed by one-way analysis of variance (ANOVA), followed by Scheffe’s procedure. The binding of IgA to CD89 expressed in MFI, was normally distributed, and consequently analysed by (two-tailed) t-test for independent samples and expressed as arithmetic means ± SEM. Binding curves of patient and normal IgA to CD89 were analysed using regression line statistics. For all tests P values <0.05 were considered significant.

Results

FACS analysis of IgA binding to nontransfected and CD89-transfected IIA1.6 cells

In order to assess binding of IgA to CD89 we used CD89-transfected IIA1.6 cells as a model [15]. These CD89-transfected IIA1.6 cells stained 100% positive for CD89 using mAb A77, whereas nontransfected cells were negative (Figure 1A). In agreement with this observation purified IgA bound strongly to CD89-transfected IIA1.6 cells, while hardly any binding was seen to nontransfected cells (Figure 1A). To confirm specificity, binding of IgA to CD89-transfected IIA1.6 cells was assessed in the presence of the inhibitory mAb My43. Addition of My43 resulted in near complete inhibition of IgA binding to cells. (A) FACS histograms of IIA1.6 control cells (left) and CD89-transfected IIA1.6 cells (right) are shown. Surface expression of CD89 was detected with mAb A77(anti-CD89) (top) and binding of polymeric IgA (50 µg/ml) to CD89 was detected with mAb 4E8 (anti-IgA) followed by Gt-anti-Ms IgG1-PE (bottom). Filled histograms represents the conjugate controls, open histograms represent either CD89 expression (top) or pIgA binding (bottom). (B) FACS histograms of CD89-transfected IIA1.6 cells are shown. IgA binding was detected as described above, using aggregated IgA (50 µg/ml) in the presence of an irrelevant IgM mAb (left) or in the presence of IgM mAb MY43 (anti-CD89) (right).

Next, we assessed the binding to CD89-transfected IIA1.6 cells of IgA directly from whole serum. Incubation of CD89-transfected IIA1.6 cells with varying dilutions of serum resulted in a dose-dependent binding of IgA to the cells. No detectable binding to nontransfected IIA1.6 cells was observed. When we studied other isotypes, we could not demonstrate any binding of IgM or IgG to CD89 transfected cells (data not shown). The binding of IgA was found to be linear in a dilution range of serum from 1/20 to 1/800 (data not shown).

Binding of IgA from patient and control sera to CD89-transfected IIA1.6 cells

To assess the binding to CD89-transfected IIA1.6 cells of IgA directly from whole serum, sera from patients with IgAN and controls were tested for binding to CD89-transfected IIA1.6 cells at a fixed dilution of 1/50 (Table 1). As shown for purified IgA preparations, also serum IgA did not show binding to nontransfected cells (data not shown). However, in all cases binding to CD89-transfected IIA1.6 cells of IgA directly from whole serum was evident. Patients with IgAN had significantly higher concentrations of IgA (1.88 ± 0.26 mg/ml vs 1.09 ± 0.08 mg/ml; P < 0.001) and IgA1 (1.65 ± 0.26 mg/ml vs 1.05 ± 0.14 mg/ml; P < 0.01) in their sera, while no significant difference was found for IgA2 (0.25 ± 0.02 mg/ml vs 0.20 ± 0.02 mg/ml; P = 0.17). Interestingly, the higher serum IgA concentrations in patients with IgAN did
Reduced binding of IgA from patients with IgAN to CD89. In order to obtain insight in the effect of size on the binding to CD89 of IgA from patients with IgAN, sera of patients and controls were first fractionated by gelfiltration chromatography (Figure 4). The percentages of polymeric, dimeric, and monomeric IgA, calculated from the IgA concentration in the sera samples after fractionation, were not different between patients and controls (Table 2). When the binding of the IgA containing fractions was assessed on CD89-transfected IIA1.6 cells, pIgA and dIgA containing fractions of patients with IgAN and not result in enhanced binding to CD89-transfected IIA1.6 cells as compared to controls (Figure 3). The binding of the IgA subclasses, IgA1 and IgA2 showed no difference between patients and controls (Table 1).

Size fractionation of serum IgA

We demonstrated previously that purified pIgA binds better to CD89 than mIgA [9]. Therefore the amount of IgA bound to CD89 is not only determined by concentrations of IgA as described above, but also by the content and ratio of polymeric, dimeric and monomeric IgA in the sera. In order to obtain insight in the effect of size on the binding to CD89 of IgA from patients with IgAN, sera of patients and controls were first fractionated by gelfiltration chromatography (Figure 4). The percentages of polymeric, dimeric, and monomeric IgA, calculated from the IgA concentration in the sera samples after fractionation, were not different between patients and controls (Table 2). When the binding of the IgA containing fractions was assessed on CD89-transfected IIA1.6 cells, pIgA and dIgA containing fractions of patients with IgAN and not result in enhanced binding to CD89-transfected IIA1.6 cells as compared to controls (Figure 3). The binding of the IgA subclasses, IgA1 and IgA2 showed no difference between patients and controls (Table 1).

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**Table 1.** IgA binding to CD89-transfected cells

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<tr>
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<th>IgA1</th>
<th>IgA2</th>
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<tbody>
<tr>
<td>Controls</td>
<td>69.59 ± 2.7</td>
<td>25.65 ± 2.3</td>
</tr>
<tr>
<td>Patients</td>
<td>70.70 ± 3.4</td>
<td>31.30 ± 2.3</td>
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Binding of serum IgA in MFI ± SEM of patients with IgAN (n = 23) and controls (n = 17) to CD89-transfected cells.

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**Table 2.** IgA size distribution from patients with IgAN and controls

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<thead>
<tr>
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<th>pIgA</th>
<th>dIgA</th>
<th>mIgA</th>
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<tbody>
<tr>
<td>Controls</td>
<td>13.36 ± 1.9</td>
<td>28.92 ± 1.4</td>
<td>57.72 ± 2.0</td>
</tr>
<tr>
<td>Patients</td>
<td>9.70 ± 1.0</td>
<td>27.92 ± 2.1</td>
<td>62.38 ± 2.9</td>
</tr>
</tbody>
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Distribution of polymeric, dimeric and monomeric IgA from fractionated sera of patients with IgAN (n = 6) and controls (n = 6) given as percentages ± SEM.
controls showed significantly higher MFI binding values compared to mIgA containing fractions. Interestingly, mIgA from patients with IgAN showed reduced MFI values compared to monomeric IgA from controls, even though the mIgA concentrations in the tested fractions of the patients with IgAN was ~3-fold higher compared to the controls (Figure 4).

**Binding of polymeric, dimeric, and monomeric IgA to CD89-transfected IIA1.6 cells**

Next we assessed binding to CD89-transfected IIA1.6 cells of peak fractions containing pIgA, dIgA and mIgA. These fractions chosen showed no overlap in size as determined by gradient gel analysis (data not shown). First these fractions were tested at a concentration of 25 μg/ml. At these fixed concentrations, mIgA of patients with IgAN showed a strongly decreased binding to CD89 as compared to controls (Figure 5A). When tested in a dose response, there was a significantly (P<0.05) lower binding (MFI) of mIgA to CD89 from patients with IgAN as compared to controls (Figure 5B). Binding to CD89-transfected IIA1.6 cells of dIgA and pIgA of patients was not significantly reduced as compared to dIgA and pIgA of controls (Figure 5C).

**Binding and inhibition of IgA to U937**

To exclude that the observed differences were caused by the cell-transfectant, similar experiments were performed with cells which naturally express CD89. For this purpose the monocytic like cell line U937 was used. Control experiments showed a significant expression of CD89 on U937 and binding of purified IgA which was completely inhibited by MY43 (data not shown). When purified fractions of monomeric IgA from patients and controls was tested for binding, we also found a significantly reduced binding of mIgA from IgAN patients (data not shown).

The reduced binding of mIgA to CD89 might lead to a reduced interference with pIgA binding and therefore favour pIgA deposition via CD89 interaction. To assess the capacity of mIgA from patients with IgAN and controls to interfere with binding of pIgA, U937 cells were pre-incubated with purified fractions of mIgA and specific binding of αIgA2 was tested. Monomeric IgA isolated from controls (n = 3) inhibited αIgA2 binding with 34.23 ± 4.43%, whereas mIgA isolated from patients with IgAN (n = 3) showed a significantly reduced inhibition of 11.68 ± 2.70% (P < 0.05) (Figure 6).

**Discussion**

In this study we assessed the binding of IgA of different sizes to IIA1.6 cells transfected with human CD89. We used either purified IgA or IgA directly from patient and control sera to assess binding to CD89. Comparison of binding between equal concentrations of serum or purified IgA to CD89 revealed a similar level of binding. This was found both for control sera and for sera of IgAN patients. Therefore we think it is unlikely that other serum proteins are affecting the binding of IgA to CD89. The advantage of this study compared
Reduced binding of IgA from patients with IgAN to CD89

Polymeric-IgA1 is considered to be a pivotal pathogenic factor in IgAN [1,2]. In contrast, in an experimental model it has been demonstrated that mIgA may protect the glomerulus against immune complexes containing pIgA [17]. In the line of our results this could imply that in patients with IgAN, a reduced binding of mIgA to CD89 might consequently result in a higher chance of binding of pIgA. Heat aggregated myeloma IgA2 (aIgA2) was used for binding to CD89 transfected cells in the absence or presence of mIgA isolated from patients with IgAN or controls. These serum IgA fractions consists for ±85% of IgA1 and therefore will not interfere with our detection system. The result, which is depicted in Figure 6, shows that indeed mIgA isolated from controls results in a significantly stronger inhibition of the aIgA2 binding, as compared to mIgA from IgAN patients. The fact that we demonstrated a comparable binding to CD89 of IgA1 and IgA2, would also imply an increased deposition of IgA2. However, it is thought that deposits of IgA in IgAN mainly consist of IgA1 [1,2].

Binding of IgA-containing immune complexes to mesangial cells induces release of inflammatory factors such as superoxide anion, platelet-activating factor (PAF), IL-6 and TNF-α [4,8,18]. The binding of IgA to mesangial cells is not solely dependent on the presence of CD89. For instance IgA or IgA-containing immune complexes can be bound via their mannose residues and targeted for endocytosis via the mannose receptor [19]. Expression of the mannose receptor on mesangial cells can be upregulated in vitro by TNF-α and IL1-α [19]. Therefore it is most likely that multiple receptors might be responsible for binding of IgA in the kidney.

An important elimination mechanism of IgA-IC in vivo next to clearance via the asialoglycoprotein receptor is thought to occur via CD89-mediated phagocytosis [4]. In IgAN patients, an impaired endocytosis of surface-bound IgA by freshly isolated monocytes and neutrophils was found after cross-linking of the IgA Fc receptors [12]. This might contribute to the higher serum IgA concentrations found in IgAN patients leading to the deposition of IgA-IC in the kidney. In addition, also CD89 on mesangial cells might be involved in clearance of deposited IgA containing immune complexes from the glomeruli, since IgA aggregates are taken up and catabolized by mesangial cells over time [18]. Therefore we think it is most likely that a failure of mesangial clearance could favor accumulation of IgA-IC on mesangial cells and thereby promote disease progression.

An aberrant interaction between IgA and its Fc receptor in IgAN patients leading to a defective clearance of IgA might be caused either by a defect in IgA or alterations of the Fc receptor. It has been demonstrated that IgA binds to CD89 via its Cζ2 and Cζ3 region [21]. Deglycosylation of the N-linked carbohydrate residues in this Cζ2 and Cζ3 region interrupts binding to CD89 [21]. In IgAN patients a lack of galactose residues in the O-linked sugars of the IgA1 hinge region has been reported [6,20,22,23]. Since these
residues are normally recognized by the asialoglycoprotein receptor, but could also be of importance for IgA interactions with CD89. This could be a possible explanation for escape of IgA containing immune complexes from effective receptor mediated clearance, thus leading to higher serum IgA levels and deposition of IgA-ICs [24,25].

Reports of recurrent IgA deposits in normal kidneys transplanted in IgAN recipients provide evidence that the basic abnormality in this condition lies within the IgA immune system rather than in the kidney [1,2]. The observation that the IgA deposits disappear when a graft containing mesangial IgA deposits is accidentally transplanted in a recipient not suffering from IgAN, further strengthens the idea that systemic factors are involved in the pathogenicity [26]. Nevertheless, alterations of CD89 expression have been described in patients with IgAN including dysfunction in vivo of CD89 on blood phagocytic cells [12]. Furthermore, the different splice variants of CD89 that have been described so far, which lack certain parts of the extracellular IgA binding domain, could possibly play a role in the pathogenesis of IgAN [4].

In conclusion we have demonstrated a significantly reduced binding to CD89 of mIgA from patients with IgAN. This might have direct consequences for the clearance of the IgA molecule. In addition because of the reduced interference with pIgA binding, this could also contribute to pIgA deposition in the kidney.

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References