Differences in glomerular leukocyte infiltration between IgA nephropathy and membranoproliferative glomerulonephritis

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Abstract

Background. An important aspect in glomerular nephritic processes is the enhanced influx of leukocytes into the glomerulus.

Methods. To investigate the mechanisms of intraglomerular leukocyte infiltration in IgA nephropathy (IgA-N) and membranoproliferative glomerulonephritis type I (MPGN-I), we immunohistochemically examined the intraglomerular expression of leukocyte function-associated antigen-1 (LFA-1, CD11a/CD18), macrophage-1 (Mac-1, CD11b/CD18) and intercellular adhesion molecule-1 (ICAM-1, CD54) together with glomerular deposition of C3c and fibrinogen.

Results. In IgA-N (n=42), LFA-1+ cells were distributed mainly in glomeruli with intense expression of ICAM-1, and there was a positive correlation (P<0.001) between the number of LFA-1+ cells and the degree of ICAM-1 expression. Mac-1+ cells had no correlation with glomerular C3c deposition, but had a significant correlation with fibrinogen deposition (P<0.05). The number of LFA-1+ cells was significantly greater than of Mac-1+ cells (P<0.05). The number of LFA-1+ cells was strongly correlated with that of CD68+ cells (P<0.00001). In MPGN-I (n=43), on the contrary, Mac-1+ cells correlated only with C3c deposition (P<0.001), and they were observed mainly in peripheral loops of glomerular capillaries where C3c was deposited with a similar distribution. However, there was no relationship between LFA-1+ cells and ICAM-1 expression. The number of Mac-1+ cells was greater than that of LFA-1+ cells (P<0.0001), and most Mac-1+ cells were identical to CD15+ cells.

Conclusion. These results indicate the possibility that different mechanisms may cause glomerular leukocyte infiltration in various forms of human glomerulonephritis. The LFA-1/ICAM-1 pathway may play an important role in glomerular leukocyte infiltration in IgA-N, while the Mac-1/complement pathway may be important in MPGN-I. The former may promote mainly the infiltration of CD68+ cells, and the latter may promote that of CD15+ cells. In addition, Mac-1+ cells may act as fibrinogen and complement receptors in IgA-N and MPGN-I, respectively.

Key words: adhesion molecules; complements; glomerular leukocytes infiltration; IgA nephropathy; membranoproliferative glomerulonephritis

Introduction

IgA nephropathy (IgA-N), first reported by Berger and Hinglais [1], is the most common type of slowly progressive glomerulonephritis characterized by mesangial proliferation and predominantly mesangial deposition of IgA. This disease is occasionally accompanied by depositions of C3c and fibrinogen. Membranoproliferative glomerulonephritis type I (MPGN-I), the most common form of MPGN, is characterized morphologically by mesangial and endocapillary proliferation associated with duplication of the capillary walls and subendothelial electron-dense deposits. The complement system is known to be closely related to the pathogenesis of this disease, since it is accompanied by hypocomplementaemia and marked C3c deposits in the peripheral capillary walls in glomeruli [2,3].

An important aspect in the pathogenesis of these two diseases is the enhanced influx of leukocytes, including the monocyte and macrophage lineage, into the glomerulus [4–8]. In IgA-N, monocytes/macrophages are involved in mesangial proliferation and the development of glomerular damage, and they are closely correlated with the degree of proteinuria [4,5]. In MPGN-I, marked glomerular infiltration of leukocytes is observed [6–8]. A recent study showed that continuous or recurrent glomerular leukocyte infiltration was associated with therapeutic resistance [7]. Leukocytes positive for macrophage-1 (Mac-1, CD11b/CD18), which has complement receptors, have an important role, since the complement system...
Leukocyte infiltration in IgA-N and MPGN

appears to be involved in the pathogenesis of MPGN [8].

Experimental studies have shown that monocytes/macrophages bind to immunoglobulin deposited in the glomerulus via their Fc receptors [9], or respond to cytokines released by sensitized T cells [10], activated complement components [11] or chemotactic fragments of fibrin or its degeneration products [12]. However, all these possible mechanisms of glomerular leukocyte infiltration remain uncertain in human proliferative glomerulonephritis.

Recently, adhesion molecules have been reported to have an important role in leukocyte infiltration into glomeruli [13,14]. Beta 2 integrins are the best studied and perhaps the most important. These consist of three members that are exclusively expressed on leukocytes and are called leukocyte function-associated antigen-1 (LFA-1, CD11a/CD18), Mac-1 (CD11b/CD18, CR3) and p150,95 (CD11c/CD18, CR4). Intercellular adhesion molecule-1 (ICAM-1), which belongs to the 2.0 mg/dl range. In addition, to characterize LFA-1+ or Mac-1+ cells further, we also used monoclonal antibodies to CD68 and CD15, which are good markers for macrophages [18] and granulocytes/macrophages [19], respectively.

Subjects and methods

Patients and renal tissues

Kidney biopsy specimens from patients with IgA-N (n = 42) and MPGN-I (n = 43) were examined (Table 1). IgA-N or MPGN-I was diagnosed by light microscopic, immunohistochemical (IgG, IgA, IgM, C1q, C3c and fibrinogen) and electron microscopic examinations according to the second edition of Renal Disease: Classification and Atlas of Glomerular Diseases published in collaboration with the World Health Organization (WHO) [20]. The diagnosis of IgA-N was based on the presence of glomerular modifications characterized by diffuse mesangial proliferation accompanied by predominant mesangial IgA deposition. MPGN-I was compatible with the presence of diffuse mesangial and endothelial proliferation associated with a lobulation of glomerular tufts and duplication of the capillary walls. Marked C3c deposition was observed in a peripheral lobular pattern on immunohistochemical examination, and subendothelial electron-dense deposits were observed on electron microscopic examination. In these cases, other diseases, e.g. systemic lupus erythematosus, Henoch–Schönlein purpura and liver diseases, were ruled out. The cases with serum creatinine levels > 2.0 mg/dl were excluded.

At the time of biopsy, the ages of the IgA-N and MPGN-I patients ranged from 7 to 51 years (23 ± 13, mean ± SD) and from 4 to 53 years (17 ± 10), respectively. In the IgA-N group, serum creatinine levels were within the normal range (< 1.2 mg/dl) in 33 of 42 patients, and ranged from 1.4 to 2.0 mg/dl in the other nine patients. In the MPGN-I group, all of the patients had a normal serum creatinine level, except one with 1.7 mg/dl. Urinary protein excretion was 2.1 ± 2.8 g/day in the IgA-N and 2.6 ± 3.0 g/day in the MPGN-I group. Hypocomplementaemia, defined as total haemolytic activities (CH50) < 30 U/ml, was observed in 38 of 42 cases examined in the MPGN-I and in one of 14 cases examined in the IgA-N group.

None of the patients were treated with steroids or other immunosuppressive drugs before biopsy.

Immunohistochemistry

For immunoperoxidase staining, all biopsy specimens were for Cytochrome oxidase (WHO) [19], respectively. embedded in paraffin at 56°C and cut into 2 μm thick sections.

The following mouse monoclonal antibodies (MoAbs) were purchased from Dako Japan Co., Ltd (Kyoto, Japan): MHM24, anti-human LFA-1; 2LPM19c, anti-human Mac-1; 6.5B5, anti-human ICAM-1; and EBM11, anti-human CD68. The monoclonal antibody to human CD15, C3D-1, was from Nippon Becton Dickinson Co., Ltd (Kyoto, Japan). Rabbit anti-human IgG, IgA, IgM, fibrinogen, C1q and C3c sera were also obtained from Dako Japan Co., Ltd (Kyoto, Japan), and were used as the primary antibodies for indirect immunoperoxidase staining. The immunoperoxidase activity was demonstrated by 0.02% 3,3′-diaminobenzidine tetrahydrochloride (DAB) in Tris–HCl buffer containing 0.01% H2O2 and 0.3% NaN3 for 10 min. After washing, sections were counterstained with Mayer’s haematoxylin, dehydrated, cleared and mounted. All incubations were performed at 37°C.

Rabbit anti-human IgG, IgA, IgM, fibrinogen, C1q and C3c sera were also obtained from Dako Japan Co., Ltd (Kyoto, Japan), and were used as the primary antibodies for indirect immunoperoxidase staining of glomerular deposits as previously described [22].

The number of glomeruli contained in each section was large enough to analyse, and ranged from 5 to 62 (17 ± 11.4, mean ± SD) in patients with IgA-N and from 6 to 60 (21 ± 12) in those with MPGN-I. Control specimens (n = 7) were obtained from normal kidneys removed for surgical reasons.

### Table 1. Patient details at biopsy

<table>
<thead>
<tr>
<th></th>
<th>IgA-N (n = 42)</th>
<th>MPGN-I (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F:M)</td>
<td>15:27</td>
<td>22:21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23 ± 13 (7–51)</td>
<td>17 ± 10 (4–53)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 ± 0.4 (0.6–2.0)</td>
<td>0.8 ± 0.3 (0.4–1.7)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>15 ± 4.0 (8–24)</td>
<td>14 ± 4.0 (7–26)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.1 ± 2.8 (0–14)</td>
<td>2.6 ± 3.0 (0–14)</td>
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<tr>
<td>Hypocomplementaemic cases</td>
<td>1*</td>
<td>38*</td>
</tr>
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</table>

*Fourteen cases were examined; 142 cases were examined. Values are expressed as mean ± SD.
To represent the severity of glomerular injury in each patient, we used the index of glomerular lesion (IGL), a semi-quantitative scoring system, which was introduced by Suwa and Takahashi [23] (Figure 2) and was applied in our previous study [8].

Histological evaluation was made independently by two pathologists without knowledge of the clinical features of the patients. Extracapillary positively stained cells, such as those found in crescents, or glomeruli which showed global sclerosis, were excluded from the count.

Statistical analysis

The correlation between the index of ICAM-1 and the number of LFA-1⁺ cells was evaluated in terms of Pearson’s correlation coefficients. The number of LFA-1⁺ cells compared with that of Mac-1⁺ cells in each disease was evaluated by Student’s t-test, and the comparison of the degree of glomerular C3c deposition with that of fibrinogen deposition in each disease was performed with the Mann–Whitney’s U

Staining intensities of C3c and fibrinogen deposition were evaluated on a semiquantitative scale from − to 3⁺.

Fig. 1. Four staining patterns obtained with anti-ICAM-1 antibody. (a; MPGN-I) grade 0; ICAM-1 is not observed in the glomerulus, but on Bowman’s capsule (arrows). (b; normal kidney) grade 1; ICAM-1 is expressed weakly by endothelial cells (small arrowheads) and some mesangial cells (large arrowheads) to the same extent as on Bowman’s capsule (arrows). (c; IgA-N) grade 2 and (d; MPGN-I) grade 3; stainings of ICAM-1 on endothelial cells and in the mesangium are slightly and markedly increased compared with those of Bowman’s capsule, respectively. Magnification ×200.
ICAM-1 was constitutively expressed in normal renal tissues with an index of 0.89±0.20 (mean±SD) (Figure 1b). It was slightly expressed by endothelial cells and some mesangial cells. The index of ICAM-1 in IgA-N was 0.15–2.9 (1.5±0.86) and that in MPGN-I was 0.32–2.4 (1.5±0.62). The index of ICAM-1 was significantly higher in both IgA-N and MPGN-I than in the normal control (P<0.01).

In IgA-N, as shown in Figure 3, numerous LFA-1+ cells were observed mainly in the glomeruli, with strong expression of ICAM-1. The number of LFA-1+ cells was positively correlated with the index of ICAM-1 (P<0.001, Figure 4a). In MPGN-I, however, there was no positive correlation between the number of LFA-1+ cells and the index of ICAM-1 (Figure 4b).

Relationship between Mac-1+ cells and C3c or fibrinogen deposition

Table 3 shows the distribution of glomerular C3c and fibrinogen deposition. The C3c deposition was more

Results

Numbers of LFA-1+ and Mac-1+ cells

In IgA-N, as shown in Table 2, there were significantly more LFA-1+ cells than Mac-1+ cells (P<0.05). In MPGN-I, by contrast, the number of Mac-1+ cells was significantly greater than of LFA-1+ cells (P<0.0001).

The severity of glomerular injury and immunohistochemistry

In both IgA-N and MPGN-I, there was no significant correlation between the IGL and the numbers of LFA-1+ and Mac-1+ cells, the index of ICAM-1, or the degrees of C3c and fibrinogen deposition. Urinary protein excretion was significantly correlated with the numbers of LFA-1+ and Mac-1+ cells in both diseases, but serum creatinine and blood urea nitrogen levels were not correlated with them (data not shown).

Table 2. Numbers of LFA-1+ and Mac-1+ cells

<table>
<thead>
<tr>
<th></th>
<th>LFA-1+ cells (cells/gcs)</th>
<th>Mac-1+ cells (cells/gcs)</th>
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</thead>
<tbody>
<tr>
<td>IgA-N (n=42)</td>
<td>5.5±4.9*</td>
<td>3.4±2.4</td>
</tr>
<tr>
<td>MPGN-I (n=43)</td>
<td>3.4±3.0</td>
<td>9.6±7.8**</td>
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<tr>
<td>Control (n=7)</td>
<td>0.3±0.02</td>
<td>0.4±0.01</td>
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</table>

*P<0.05 vs Mac-1+ cells; **P<0.0001 vs LFA-1+ cells.

gcs, glomerular cross-section. Values are expressed as mean±SD.
Fig. 4. Relationship between the index of ICAM-1 and the number of LFA-1$^+$ cells. (a) There was a positive correlation between the index of ICAM-1 and the number of LFA-1$^+$ cells in IgA-N, (b) but not in MPGN-I gcs. glomerular cross-section; NS, not significant.

Table 3. Glomerular deposition of C3c and fibrinogen

<table>
<thead>
<tr>
<th></th>
<th>IgA-N ($n=42$)</th>
<th>MPGN-I ($n=43$)</th>
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<tbody>
<tr>
<td>C3c$^*$</td>
<td>8</td>
<td>0</td>
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<tr>
<td>+</td>
<td>12</td>
<td>7</td>
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<td>++</td>
<td>20</td>
<td>18</td>
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<td>+++</td>
<td>2</td>
<td>18</td>
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<tr>
<td>Fibrinogen</td>
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<td></td>
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<tr>
<td>−</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>+</td>
<td>9</td>
<td>21</td>
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<tr>
<td>++</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>+++</td>
<td>6</td>
<td>2</td>
</tr>
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</table>

Number of cases in each grade of deposition.

$^*$P < 0.0001 IgA-N vs MPGN-I.

pronounced in MPGN-I than in IgA-N. However, there was no difference in the fibrinogen deposition between IgA-N and MPGN-I.

In MPGN-I, Mac-1$^+$ cells were observed mainly in peripheral loops of glomerular capillaries, similar to the distribution of glomerular C3c deposition (Figure 5). The number of Mac-1$^+$ cells correlated with the degree of glomerular C3c deposition ($P < 0.001$), but not with that of glomerular fibrinogen deposition (Table 4). In IgA-N, on the contrary, the number of Mac-1$^+$ cells did not correlate with the degree of glomerular C3c deposition, but correlated with that of fibrinogen deposition ($P < 0.05$; Table 4).

$CD15^+$ and $CD68^+$ cells

Table 5 shows the correlation between the numbers of LFA-1$^+$ or Mac-1$^+$ cells and CD15$^+$ or CD68$^+$ cells. In IgA-N, LFA-1$^+$ cells had a positive correlation with CD68$^+$ cells ($r=0.74$, $P<0.00001$), but not with CD15$^+$ cells ($r=0.10$, NS). Mac-1$^+$ cells were positively correlated with both CD15$^+$ and CD68$^+$ cells, and the correlation was stronger between Mac-1$^+$ and CD68$^+$ cells ($r=0.66$, $P<0.00001$) than between Mac-1$^+$ and CD15$^+$ ($r=0.48$, $P<0.001$).

In MPGN-I, on the other hand, LFA-1$^+$ cells had a positive correlation with both CD15$^+$ ($r=0.51$, $P<0.001$) and CD68$^+$ cells ($r=0.55$, $P<0.001$). Mac-1$^+$ cells showed a strongly positive correlation with CD15$^+$ cells ($r=0.95$, $P<0.00001$), but not with CD68$^+$ cells ($r=0.25$, NS). On mirror section staining, most of Mac-1$^+$ cells were found to be identical to CD15$^+$ cells (Figure 6).
Leukocyte infiltration in IgA-N and MPGN

Table 4. Correlations between the number of Mac-1$^+$ cells and the degree of glomerular C3c and fibrinogen deposition

<table>
<thead>
<tr>
<th></th>
<th>IgA-N ($n=42$)</th>
<th>MPGN-I ($n=43$)</th>
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<tbody>
<tr>
<td></td>
<td>C3c Fibrinogen</td>
<td>C3c Fibrinogen</td>
</tr>
<tr>
<td>Mac-1$^+$ cells</td>
<td>$r=0.05$ $P&lt;0.05$</td>
<td>$r=0.59$ $P&lt;0.001$</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>P</td>
</tr>
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</table>

Discussion

Recent studies have demonstrated that infiltrating glomerular leukocytes, especially monocytes/macrophages, contribute to glomerular nephritic processes [4–8]. Experimental studies have shown that the infiltration of monocytes/macrophages into glomeruli occurs in several ways; (i) binding to immunoglobulin deposited within glomeruli via their Fc receptors [9]; (ii) responding to chemotactic factors released by sensitized T cells [10]; or (iii) responding to activated complement components [11] or chemotactic peptide arising from fibrin degeneration [12]. In the present human study, we observed that the mechanism of glomerular leukocyte infiltration may differ between IgA-N and MPGN-I. In IgA-N, leukocyte infiltration occurs mainly through LFA-1/ICAM-1 interaction, while Mac-1/complement interaction is involved in MPGN-I. LFA-1 and Mac-1 are adhesion molecules belonging to the $\beta$2 integrin family. LFA-1 is expressed on most leukocytes [24], and is the counter-receptor for ICAM-1 which is a member of adhesion molecules belonging to the immunoglobulin superfamily and is expressed mainly on endothelial and epithelial cells [15,16]. Mac-1 is expressed predominantly on granulocytes/monocytes [25], and has binding sites for C3b inactivator-cleaved C3b (C3bi) [16].

Monoclonal antibody EMB11 (CD68) stains macrophages in a wide variety of human tissues [18]. Neutrophils react only weakly with this antibody [26]. Monoclonal antibody C3D-1 (CD15) recognizes granulocytes/monocytes, and does not react with macrophages [19]. Our present study showed that in IgA-N, LFA-1$^+$ cells were mainly CD68$^+$ macrophages, and Mac-1$^+$ cells belonged to both CD15$^+$ granulocytes/monocytes and CD68$^+$ macrophages. In MPGN-I, in contrast, Mac-1$^+$ cells were CD15$^+$ granulocytes/monocytes, and LFA-1$^+$ cells belonged to both CD15$^+$ granulocytes/monocytes and CD68$^+$ macrophages. These results indicate the possibility that the nature of LFA-1$^+$ or Mac-1$^+$ cells varies among various forms of glomerulonephritis.

The importance of LFA-1/ICAM-1 interaction has been reported in leukocyte accumulation and glomerular damage in experimental anti-glomerular basement membrane glomerulonephritis [14] and in non-human primates with renal allograft [27]. In humans, Canton

Table 5. Correlations between the number of LFA-1$^+$ or Mac-1$^+$ cells and that of CD15$^+$ or CD68$^+$ cells

<table>
<thead>
<tr>
<th></th>
<th>IgA-N</th>
<th>MPGN-I</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CD15$^+$ cells</td>
</tr>
<tr>
<td>LFA-1$^+$ cells</td>
<td>$r=0.10$</td>
<td>$r=0.74$</td>
</tr>
<tr>
<td>NS</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Mac-1$^+$ cells</td>
<td>$r=0.48$</td>
<td>$r=0.66$</td>
</tr>
<tr>
<td>$P&lt;0.001$</td>
<td>$P&lt;0.00001$</td>
<td>$P&lt;0.0001$</td>
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</table>

NS, not significant.
et al. reported that intense de novo mesangial expression of ICAM-1 in primary focal segmental glomerulosclerosis indicates the activation of mesangial cells, possibly associated with local release of cytokines [28]. Lhotta et al. reported that increased glomerular expression of ICAM-1 was observed in early cases of rapidly progressive glomerulonephritis (RPGN), lupus nephritis and in some cases of IgA-N, and that a decrease in ICAM-1 expression was noted in membranous nephropathy, MPGN and in advanced RPGN [29].

However, the participation of LFA-1+ cells or the interaction between LFA-1 and ICAM-1 was not examined in these studies, and it is still uncertain whether or not LFA-1/ICAM-1 interaction really participates in the mechanism of glomerular leukocyte infiltration in human glomerulonephritis. Recently, Tomino et al. reported that the expression of ICAM-1 was closely linked to intraglomerular infiltration of lymphocytes and monocytes and cell proliferation in IgA-N [30]. This study strongly supports our conclusion that LFA-1/ICAM-1 interaction actually contributes to the glomerular infiltration of LFA-1+ leukocytes in IgA-N.

In IgA-N, LFA-1+ cells were mainly macrophages. Macrophages are thought to contribute to the pathogenesis of IgA-N by producing cytokines, such as interleukin-1, interleukin-6 and tumour necrosis factor, which mediate mesangial cell proliferation [31–33].

We recently reported that the number of intraglomerular monocytes/macrophages was reduced chronologically in association with a decrease in glomerular C3c deposition in repeat biopsies of patients with MPGN-I [7]. We hypothesized that the chronological reduction in infiltrating glomerular leukocytes probably indicated a decrease in leukocytes bearing complement receptors. In the current study, we obtained evidence that Mac-1 antigen, which has binding sites for C3bi and is called complement receptor 3 (CR3), plays an important role in the glomerular infiltration of granulocytes/monocytes through the interaction with glomerular C3c deposits. Infiltrating granulocytes/monocytes produce reactive oxygen species [34] and proteolytic enzymes, such as elastase, cathepsin G and lysozome [35], which mediate glomerular injury [36]. Recently, it has been shown that activated CD8+ T cells also express Mac-1, and that the expression of Mac-1 facilitates T-cell homing to sites of inflammation [37]. In a recent study of ours, a significant increase in glomerular T cells as well as granulocytes/monocytes was observed in MPGN-I [7]. Influx of granulocytes/monocytes into glomeruli could contribute to glomerular injury by the production of reactive oxygen species or proteolytic enzymes as well as an increased number of T cells in glomeruli.

Although a minor population, a considerable number of glomerular Mac-1+ cells and CD68+ macrophages was observed in IgA-N and MPGN-I, respectively. In IgA-N, Mac-1+ cells correlated with the degree of fibrinogen deposition (Table 4). Mac-1 antigen has binding sites for fibrinogen as well as for C3bi [17], and a close relationship between monocyte infiltration and cross-linked fibrin deposition was reported in IgA-N [38]. Therefore, Mac-1+ cells may act as fibrinogen receptors in IgA-N. On the other hand, we recently reported that marked p150,95+ cell infiltration was observed in MPGN-I which dramatically decreased associated with a decrease in glomerular C3c deposits [7]. p150,95 (CD11c/CD18, CR4), which is another member of the β2 integrin family, has been reported to be expressed on monocytes/macrophages and to be the receptor for C3bi [16]. p150,95 antigen may be involved in the glomerular infiltration of macrophages in MPGN-I.

Why do Mac-1+ cells act as complement receptors in MPGN-I, but as fibrinogen receptors in IgA-N? Glomerular C3c deposits are observed mainly in peripheral loops of glomerular capillaries in a similar distribution as Mac-1+ cells in MPGN-I, whereas they are observed in the mesangium in IgA-N. This fact

<table>
<thead>
<tr>
<th>Interaction</th>
<th>IgA-N</th>
<th>MPGN-I</th>
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<tbody>
<tr>
<td>LFA-1+ cells = ICAM-1</td>
<td>LFA-1+ cells = ICAM-1</td>
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<tr>
<td>CD15, CD68</td>
<td>Mac-1+ cells = C3c</td>
<td></td>
</tr>
<tr>
<td>Mac-1+ cells = fibrinogen</td>
<td>Mac-1+ cells = C3c</td>
<td></td>
</tr>
<tr>
<td>LFA-1+ cells &gt; Mac-1+ cells</td>
<td>Mac-1+ cells &gt; LFA-1+ cells</td>
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</tbody>
</table>

Table 6. Differences in the mechanism of glomerular leukocyte infiltration between IgA-N and MPGN-I

<table>
<thead>
<tr>
<th>Cell distribution</th>
<th>IgA-N</th>
<th>MPGN-I</th>
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<tr>
<td>LFA-1+ cells = CD15</td>
<td>LFA-1+ cells = CD15 and CD68</td>
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<tr>
<td>LFA-1+ cells = CD68</td>
<td>Mac-1+ cells = CD15</td>
<td></td>
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<tr>
<td>Mac-1+ cells = CD15 and CD68</td>
<td>Mac-1+ cells = CD15</td>
<td></td>
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</table>

Table 7. Differences in cell distribution between IgA-N and MPGN-I
Leukocyte infiltration in IgA-N and MPGN emphasizes the importance of the interaction between Mac-1\(^+\) cells and endothelial cells or subendothelial deposits. However, we could not explain clearly why Mac-1\(^+\) cells act as fibrinogen receptors only in IgA-N. A recent study showed that ICAM-1 expressed on vascular endothelium plays an important role in the adhesion of Mac-1\(^+\) cells to vascular endothelium through fibrinogen [39]. In our study, Mac-1\(^+\) cells showed a significant correlation with the degree of ICAM-1 in IgA-N, but not in MPGN-I (data not shown). These differences may be related to the variability in the function of Mac-1 antigen.

In conclusion, as summarized in Tables 6 and 7, different mechanisms may cause the glomerular leukocyte infiltration in IgA-N and MPGN-I. In IgA-N, the LFA-1/ICAM-1 interaction, which promotes the infiltration of macrophages, plays an important role in glomerular leukocyte infiltration. In contrast, in MPGN-I, the Mac-1/complement interaction is important and it promotes the glomerular infiltration of granulocytes/macrophages. In addition, there is a possibility that Mac-1\(^+\) cells act as fibrinogen and complement receptors in IgA-N and MPGN-I, respectively. However, it is uncertain whether or not the LFA-1/ICAM-1 and Mac-1/complement interactions are unique phenomena in IgA-N and MPGN-I, respectively. Further examinations are warranted in other glomerular diseases such as focal segmental glomerulosclerosis, rapidly progressive glomerulonephritis and lupus nephritis.

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