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*J Immunol* 2000; 165:1387-1394; doi: 10.4049/jimmunol.165.3.1387
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Increased Frequency of Surface IgA-Positive Plasma Cells in the Intestinal Lamina Propria and Decreased IgA Excretion in Hyper IgA (HIGA) Mice, a Murine Model of IgA Nephropathy with Hyperserum IgA

Tadashi Kamata,*† Fumiaki Nogaki,** Sidonia Fagarasan,* Toshio Sakiyama,* Ikee Kobayashi,† Shigeki Miyawaki,‡ Koichi Ikuta,* Eri Muso,† Haruyoshi Yoshida,§ Shigetake Sasayama,† and Tasuku Honjo2*

Because abnormalities of mucosal immunity have been suggested in human IgA nephropathy, we examined the involvement of mucosal immunity in IgA deposition to the kidney in hyper IgA (HIGA) mice, which was established as a mouse model for human IgA nephropathy with hyperserum IgA. The number of surface IgA+B220− lymphocytes in the intestinal lamina propria (LP) of HIGA mice increased 2.7-fold at 30 wk of age as compared with those at 10 wk of age, whereas normal mice did not show such increase. The surface IgA+B220− LP lymphocytes spontaneously secreted IgA in culture. Morphological studies showed that the surface IgA+B220− lymphocytes of murine intestinal LP are identical with plasma cells (PCs). About 20% of IgA+B220− PC in LP expressed both Mac-1 and CD19, suggesting that they may derive from peritoneal B-1 cells. Cell cycle study on intestinal IgA-PCs using bromodeoxyuridine revealed no difference between HIGA mice and normal mice, suggesting that the high frequency of IgA-producing PCs in HIGA mice is not due to enhanced proliferation or prolonged survival of IgA-producing PCs in LP. In addition, IgA secretion into the gut lumen of HIGA mice decreased drastically (to one forth) with aging. These data suggest that the increased number of intestinal IgA-producing PCs and the down-regulation of IgA excretion into the intestinal lumen might synergistically contribute to the hyperserum IgA in HIGA mice and resultant IgA deposition to the kidney. The Journal of Immunology, 2000, 165: 1387–1394.

IgA nephropathy is the most common form of human glomerulonephritis worldwide, characterized by the deposition of IgA in the glomeruli (9). Although the mechanism of human IgA nephropathy has not been fully elucidated, high serum IgA levels, enhanced IgA-specific Th cells, and diminished numbers of IgA-specific regulatory T cells suggest that there is a basic dysregulation of IgA production in patients with this disease (10, 11). Moreover, clinical association of relapses with mucosal infections, elevated serum Ab titers to respiratory pathogens, and dietary components in these patients indicate that mucosal immunity may also be involved in the pathogenesis of IgA nephropathy (12, 13). DdY mice are known to be a spontaneous murine model of human IgA nephropathy (14). A correlation between serum levels of IgA and extents of glomerular IgA deposition has been reported.

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Received for publication November 17, 2000. Accepted for publication May 11, 2000.

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1 This work was partly supported by a Center of Excellence Grant (07CE2005) and a Grant-in-Aid for General Scientific Research (10044275) from the Japanese Ministry of Education, Science, and Culture.

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3 Abbreviations used in this paper: LP, lamina propria; HIGA, hyper IgA; mIgA, membranous IgA; PCs, plasma cells; IgA-PCs, IgA-producing PCs; PP, Peyer’s patches; BrdU, bromodeoxyuridine; pIgR, polymeric Ig receptor; ELISPOT, enzyme-linked immunospot.

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for ddY mice (15). However, incidence of the disease of outbred ddY mice is not very high and its course is highly variable, which may be due to its genetic heterogeneity.

Hence, in an attempt to obtain a genetically uniform model, an inbred strain designated hyper IgA (HIGA) mice was previously established through selective breeding of ddY mice (16, 17). We reported that HIGA mice have phenotypes such as hyperserum IgA and glomerulitis with IgA deposition that mimic human IgA nephropathy.

To understand mechanisms for hyperserum IgA in HIGA mice, we examined the involvement of mucosal immunity and found that IgA-PCs in the intestinal LP of HIGA mice increased with age in parallel with the development of hyperserum IgA. In addition, IgA secretion into the gut lumen was also impaired with age. Combination of these two abnormalities appears to lead to hyperserum IgA in HIGA mice.

Materials and Methods

Mice

HIGA mice were established by selective mating of high serum IgA ddY mice (17). BALB/c and C57BL/6 mice were obtained from Japan SLC (Shizuoka, Japan). These mice were maintained in horizontal laminar flow cabinets and provided food and water ad libitum. All mice used in this study were female and 10 or 30 wk of age.

Abs and surface staining

The following Abs were used for FACS analysis: FITC- or PE-labeled goat anti-mouse IgA (Southern Biotechnology Associates, Birmingham, AL); FITC- anti-mouse B220 (PharMingen, San Diego, CA); PE-anti-mouse CD23 (PharMingen); PE- anti-mouse CD5 (PharMingen); PE-APC-anti-mouse IgM (PharMingen); PE-anti-mouse Mac-1 (PharMingen); PE-anti-mouse Syndecan (PharMingen); CD23 (PharMingen); PE-anti-mouse CD5 (PharMingen); PE- or APC-labeled polyclonal Abs to mouse IgG and IgM (150 kDa) and IgE (90 kDa) were used as molecular mass markers.

Analysis of mRNA levels

Total RNA from the intestine and liver was extracted using TriZol (Life Technologies, Rockville, MD) according to the instructions of manufacturer. For Northern hybridization analysis, 15 μg of RNA were electrophoresed, transferred to a Hybond-N+ membrane (Amersham, Buckinghamshire, U.K.), and probed with randomly primed 32P-labeled mouse cDNA for the polymeric Ig receptor (pIgR).

Results and Discussion

Higher frequency of surface IgA-positive cells in intestinal LP of HIGA mice

We have shown that unlike normal mice, serum IgA levels of HIGA mice markedly increase with age (16). Serum IgA in rodents has been suggested to originate in large part from polymeric IgA produced in the intestine (3). Therefore, we examined whether the IgA production increased in LP of HIGA mice. Interestingly, FACs analysis revealed the presence of a large number of IgA B220 + cells in the intestinal LP of BALB/c, C57BL/6, and HIGA mice (Fig. 1A). The light scatter profile of the LP lymphocytes in HIGA mice showed that IgA B220 + cells (Fig. 1B, 3) were larger than B220 + lymphocytes (Fig. 1B, 1). IgA B220 + cells had somewhat higher autofluorescence than small resting cells (data not shown). The majority of B220 + cells were Igm +, and only a small number of IgA B220 + cells were found in LP. IgA B220 + cells were comprised of T cells, granulocytes, and macrophages (data not shown).

The frequency of the IgA B220 + LP lymphocytes in HIGA mice increased with age and reached the level of about 2.5 times higher than BALB/c or C57BL/6 at the age of 30 wk (Fig. 1C). The differences were more marked when the absolute numbers of IgA B220 + cells per body weight were compared (Fig. 1D). The number of IgA B220 + LP lymphocytes in HIGA mice increased 2.7-fold at 30 wk of age as compared with that at 10 wk of age. Because a considerable fraction of IgA-producing cells in LP has been shown to derive from the Ag-specific IgA-committed B cells in PP, we examined whether the frequency of IgA + B cells in PP increased in HIGA mice. As shown in Fig. 1E, IgA B220 + cells constituted <1% of LP lymphocytes, whereas PP lymphocytes contained about 8% IgA B220 + cells, which were scarce in LP lymphocytes. IgA B220 + PP cells were lower at 10 wk of age but...
May-Gru¨nwald-Giemsa staining revealed that most of the cells were detected by May-Gru¨nwald-Giemsa and cytoplasmic IgA staining. IgA+ B220− cells were isolated from HIGA and control mice by a cell sorter and examined by FACS. The frequency (C) and the absolute number (D) of IgA+ LP lymphocytes of 10- and 30-wk-old mice. The absolute number is expressed as per body weight (gram). E. A representative FACS profile of PP from 30-wk-old mice. IgA+ B220− cells are <1% in all mice tested. F. The frequency of IgA+ B220− cells in PP of 10- and 30-wk-old mice. Contrary to normal mice, IgA+ B220− cells of HIGA mice significantly increased with age. Values are the mean ± SEM from five mice. The Student t test for unpaired data was used to compare the values between the different groups; p < 0.05 was considered statistically significant. *1, p = 0.0006; *2, p < 0.0001; *3, p = 0.0006; *4, p = 0.01; *5, p = 0.02; *6, p = 0.04; *7, NS; *8, NS; *9, p = 0.02.

Identification of IgA+ B220− LP lymphocytes as PC

To characterize the IgA+ B220− LP lymphocytes, these cells were isolated from HIGA and control mice by a cell sorter and examined by May-Gru¨nwald-Giemsa and cytoplasmic IgA staining. May-Gru¨nwald-Giemsa staining revealed that most of the IgA+ B220− LP lymphocytes displayed a typical PC morphology, including an eccentric nucleus, low nuclear-to-cytoplasmic ratio, a dark basophilic cytoplasm, and a pale perinuclear compartment (Fig. 2, A–C). Nearly all of these cells contained a large amount of IgA in their cytoplasm (Fig. 2, D–F). Importantly, these cells specifically exist in the IgA+ B220− compartment because <3% of cells sorted from the other compartment showed PC morphology (data not shown). The ability of the IgA+ B220− LP lymphocytes to secrete IgA was shown by the ELISPOT assay (Table I). The frequency of the IgA+ B220− LP lymphocytes detected by FACS correlated well with that of IgA-secreting LP lymphocytes detected by the ELISPOT assay regardless of their strain difference, indicating that the IgA+ B220− LP lymphocytes spontaneously secrete IgA and fulfill the functional as well as morphological criteria of PC.

We next investigated whether IgA+ B220− PC are also detectable in other lymphoid tissues by FACS. We found that the frequency of IgA+ B220− cells were <1% in PP (Fig. 1E), spleen, and mesenteric lymph node (Fig. 3). However, May-Gru¨nwald-Giemsa and cytoplasmic IgA staining of sorted IgA+ B220− spleen cells showed that >90% of them are IgA-PCs (Fig. 4, A–C), while virtually no IgA-PCs were detected in the other sorted compartments (data not shown). In PP and mesenteric lymph nodes, we detected the same frequency of IgA+ PCs by cytoplasmic staining as that of IgA+ B220− cells (data not shown), indicating that IgA+ B220− PC are commonly found in lymphoid tissues. Although there are a few reports that PCs can express Ig on their surface (24), our observation that virtually all the IgA-PCs definitely express high levels of IgA on their surface is obviously contradictory to the generally accepted idea that PCs express little or no Ig on their surface (26). One possible explanation for this discrepancy may be that most of the previous studies were not performed on freshly isolated PCs but on cultured plasmacytomas or plasmacytoid cell lines. Another possible explanation might be that in FACS analysis, a strict light scatter gate to exclude
granulocytes and macrophages might have also excluded IgA-PCs. Indeed, the light scatter profiles of the IgA-PCs and macrophages overlap each other in part (Fig. 1B). We did not find B-1 cells in LP although previous studies including our own report indicate that LP of the gut contained B-1 cells (27–29). We speculate that these results were due to contamination of LP lymphocytes with other cells in gut-associated lymphoid tissue or misinterpretation of FACS profiles.

**Surface markers of B220^{−}IgA^{+} PC in LP**

To investigate the origin of the increased IgA-PCs in HIGA mice, we checked the frequency of B-1 cells in the peritoneal cavity because many studies indicate that peritoneal B-1 cells migrate to LP of the gut (6). The frequency of B-1 cells (CD5^{+}IgM^{high} cells) in the peritoneal cavity was lower in HIGA mice than in BALB/c or C57BL/6 mice at 10 wk of age and became comparable among the three mouse strains at 30 wk because of its reduction in BALB/c and C57BL mice (Fig. 5A). Essentially identical results were obtained when B-1 cells were defined as Mac-1^{low}IgA^{+} cells (Fig. 5B). We then examined typical surface markers of peritoneal B-1 cells and found that IgD, CD23, and CD5 were negative on IgA^{+}PC in LP (Fig. 6, B–D). Interestingly, a small fraction (about 20–25%; Table I) of IgA^{+}PC was stained weakly with anti-Mac-1 Ab (Fig. 6, E and J). CD19, a membrane protein of the Ig superfamily, is expressed only on B lymphocytes and lost on terminally differentiated PCs (30). IgA^{+}PCs were divided into CD19-positive and -negative subpopulations, suggesting that IgA^{+}PCs in the intestinal LP consist of relatively immature (CD19^{−}) and mature (CD19^{+}) PCs (Fig. 6G). As shown in Fig. 6, J and K, the majority (about 75%) of Mac-1^{low}IgA^{+}PC expressed CD19, suggesting that CD19^{+}Mac-1^{low}IgA^{+}PC may represent immature precursors to PC derived from peritoneal B-1 cells and further maturation into CD19^{−}IgA^{+}PC may also lose Mac-1, a marker of peritoneal B-1 cells.

**Table I. Correlation between the frequency of surface IgA^{+} cells detected by FACS and that of IgA-secreting cells detected by ELISPOT assay**

<table>
<thead>
<tr>
<th>Mice</th>
<th>IgA-Secreting Cells (%) (A)</th>
<th>IgA^{+} Cells (%) (B)</th>
<th>A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGA-1</td>
<td>32.3</td>
<td>35.0</td>
<td>0.92</td>
</tr>
<tr>
<td>HIGA-2</td>
<td>40.3</td>
<td>40.3</td>
<td>1.00</td>
</tr>
<tr>
<td>HIGA-3</td>
<td>36.7</td>
<td>43.1</td>
<td>0.85</td>
</tr>
<tr>
<td>HIGA-4</td>
<td>20.0</td>
<td>24.8</td>
<td>0.81</td>
</tr>
<tr>
<td>BALB/c-1</td>
<td>7.4</td>
<td>8.7</td>
<td>0.85</td>
</tr>
<tr>
<td>BALB/c-2</td>
<td>14.1</td>
<td>13.0</td>
<td>1.08</td>
</tr>
<tr>
<td>BALB/c-3</td>
<td>17.3</td>
<td>15.4</td>
<td>1.12</td>
</tr>
<tr>
<td>BALB/c-4</td>
<td>7.1</td>
<td>8.1</td>
<td>0.88</td>
</tr>
<tr>
<td>C57BL/6-1</td>
<td>14.5</td>
<td>17.0</td>
<td>0.85</td>
</tr>
<tr>
<td>C57BL/6-2</td>
<td>13.1</td>
<td>12.4</td>
<td>1.06</td>
</tr>
<tr>
<td>C57BL/6-3</td>
<td>10.0</td>
<td>14.1</td>
<td>0.71</td>
</tr>
<tr>
<td>C57BL/6-4</td>
<td>14.6</td>
<td>16.2</td>
<td>0.90</td>
</tr>
</tbody>
</table>

* Frequency of surface IgA positive cells detected by FACS. A good and significant correlation was noted between the frequency of surface IgA^{+} cells detected by FACS and that of IgA-secreting cells detected by ELISPOT assay ($r = 0.98$, $p < 0.0001$). The age of the mice is 30 wk.
CD38 is a transmembrane glycoprotein that is widely expressed on cells of hemopoietic and nonhemopoietic lineages. FACS analysis (Fig. 6H) revealed that IgA

1

PCs strongly express CD38. CD38 expression on PCs is reported to be different between mouse and human: the expression levels of human CD38 decrease during B cell development and increase on PCs (25). In contrast, CD38 expression was reported to be down-regulated in mouse PCs (33). Although the present result contradicts the previous report, characterization of PC in the previous report was not definitive because they assumed that B220

2

cells found in in vitro LPS-stimulated spleen cells are PC. The IgA

1

PCs do not express CD40 (Fig. 6I), which is a member of the TNF receptor family expressed predominantly on cells of the B cell lineage (34, 35). Virtually identical results were obtained on IgA

1

PCs in LP of BALB/c and C57BL/6 mice (data not shown). Collectively, although the relative contribution of two lineages, namely IgA-committed B cells in PP and peritoneal B-1 cells, to the increased IgA-PCs in HIGA mice cannot be determined precisely, the presence of a significant fraction (~25%) of IgA Mac1

low

PCs in LP of HIGA supports the previous reports that peritoneal B1 cells contribute at least in part to the formation of LP B cells (7, 8).

Cell cycle analysis of IgA-PCs in LP

Besides migration of the precursors, the frequency of the IgA-PCs may depend upon their proliferation and life span in LP. Accordingly, we analyzed the cell cycle of IgA-PCs using BrdU labeling in vivo. HIGA and C57BL/6 mice at 30 wk of age were fed with BrdU in drinking water for 20 days (pulse period). Thereafter, BrdU was removed from the drinking water (chase period). Fig. 7 shows the frequency of BrdU incorporated IgA-PCs in intestinal LP lymphocytes. The frequency of BrdU incorporated IgA-PCs reached a plateau of 20% 10 days after the initiation of BrdU administration. Some 80% of IgA-PCs did not enter the cell cycle during the pulse period of 20 days, indicating that the majority of IgA-PCs are not dividing in LP. BrdU-incorporated IgA-PCs reduced rapidly after the removal of BrdU, and most of the labeled cells disappeared on a chase period of 30 days. This is in reasonable accordance with previously reported cell kinetics study on LP lymphocytes (36). Essentially no difference was observed between the two different mouse strains, indicating that the high frequency of IgA-PCs in HIGA mice is not due to enhanced proliferation or prolonged survival of IgA

1

cells in LP.

IgA secretion in fecal extract

The level of serum IgA is considered to be dependent not only on the production and catabolism but also on the excretion into the gut lumen via intestinal epithelium and biliary tract (37). Hence, we determined the IgA levels of fecal extracts (Fig. 8). At 10 wk of age, HIGA mice had significantly higher levels of fecal IgA than BALB/c and C57BL/6. In contrast, the IgA secretion level in HIGA mice decreased drastically (one-fourth) with aging. Although we have not assessed the metabolic rates of circulating IgA, these data suggest that the increased number (2.7-fold) of intestinal IgA-PCs secreting IgA and the down-regulation of IgA excretion into the intestinal lumen might synergistically contribute to the increase (10-fold) in the serum polymeric IgA levels in HIGA mice at 30 wk of age.

---

**Figure 4.** The IgA

1

B220

2

cells in spleen are PCs. IgA

1

B220

2

splenic cells of a HIGA mouse were sorted and stained by May-Grünwald-Giemsa (A), cytoplasmic IgA (B), or 4',6'-diamidino-2-phenylindole (C). The same methods described in Fig. 2 were used. Essentially identical results were observed for BALB/c mice (data not shown).

**Figure 5.** The frequency of the B-1 cells in the peritoneal cavity. Peritoneal B-1 cells were defined as CD5

- IgM

high (A) or Mac-1

+ IgM

high (B). The same statistical analysis was done as Fig. 1. In contrast to normal mice, B-1 cells of HIGA mice do not decrease with age regardless of the definition of B-1 cell. *1, p = 0.049; *2, p = 0.002; NS; *4, p = 0.002; *5, p = 0.010.

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(44x312) (Fig. 6 F). CD38 is a transmembrane glycoprotein that is widely expressed on cells of hemopoietic and nonhemopoietic lineages. FACS analysis (Fig. 6 F) revealed that IgA

1

PCs strongly express CD38. CD38 expression on PCs is reported to be different between mouse and human: the expression levels of human CD38 decrease during B cell development and increase on PCs (25). In contrast, CD38 expression was reported to be down-regulated in mouse PCs (33). Although the present result contradicts the previous report, characterization of PC in the previous report was not definitive because they assumed that B220

- cells found in in vitro LPS-stimulated spleen cells are PC. The IgA

1

PCs do not express
IgA polymer formation and pIgR expression in HIGA

The size fractionation of serum IgA by HPLC showed that polymeric IgA is predominant as compared with those of C57BL/6 and BALB/c (Fig. 9), suggesting that increased IgA in the serum of HIGA mice could be derived from mucosal tissues. In addition, the expression of the J chain appears to be normal.

Expression of pIgR

We finally analyzed the expression levels of pIgR because pIgR is responsible for the specific transport of polymeric IgA to external mucosal surfaces (38). As shown in Fig. 10, the expression levels of pIgR mRNA did not differ among the aged mice strains both in the small intestine and the liver.

Coda

In the present study, we showed that IgA-PCs in the intestinal LP of HIGA mice but not other strains increased with age (Fig. 1, C and D). Indeed, the frequency of the IgA-PCs in RF/J mice (39), another strain of hyper IgA mice, is comparable to that of HIGA mice, whereas such cells are virtually absent in the LP of aly mice (our unpublished data), a strain that has severely reduced levels of serum IgA (40). These results suggest that the frequency of IgA-PCs in the intestinal LP is a critical determinant of the serum IgA level in rodents. In addition, our present study showing a striking increase of polymeric IgA in aged HIGA mice further indicates that IgA-PCs in the LP is the source of the increased serum IgA in HIGA mice because polymeric IgA is produced predominantly in the gut-associated lymphoid tissues (3). Since polymeric IgA is efficient in forming immune complexes because of its multivalent property, the increase of polymeric serum IgA of HIGA mice could lead to the development of circulating macromolecular complexes, which are subsequently entrapped in the kidney because of their size or via specific binding to potential IgA receptors on mesangial cells in the kidney (41).

We also showed the age-related down-regulation of IgA excretion into the intestinal lumen in HIGA mice (Fig. 8). It might reflect some deteriorated function of intestinal epithelial cells such as IgA transcytosis via the polymeric Ig receptor and proteolytic cleavage of the receptor that enables the release of its IgA-bound...
extracellular domain into the mucosal secretions. The plgR-deficient mice (38) and J chain-deficient mice (37) are reported to have elevated serum IgA levels and decreased fecal IgA levels. There were no differences in the level of plgR mRNA in the liver or small intestine of HIGA mice as compared with C57BL/6 or BALB/c mice (Fig. 10). The sequence of plgR from HIGA mice (data not shown) revealed a single nucleotide polymorphism as compared with the published sequence (42), but this change did not alter the amino acid sequence of the plgR protein. However, we did not assess J chain, which is necessary for IgA polymerization and its stable association with plgR (43). Predominant polymeric IgA in HIGA serum suggests that the J chain synthesis is not disturbed in HIGA mice.

Taken together, the chronological association of the above-mentioned IgA-related parameters strongly suggests that serum IgA and IgA deposition in the kidney originate from the intestinal LP in HIGA mice (Table II). Although whether IgA deposition in the kidney of IgA nephropathy patients originates from mucosa or bone marrow still remains a point of controversy (44), the HIGA mouse model seems to represent the former possibility.

![Image](https://example.com/image.png)

**FIGURE 9.** HPLC fractionation profiles of IgA in sera. IgA levels in fractionated samples from sera were determined by ELISA. Polymers of IgA are predominant in sera of HIGA mice as compared with BALB/c and C57BL/6 mice. Mice were 30 wk old.

**FIGURE 10.** Northern blot analysis of plgR mRNA. Total RNA (15 μg) extracted from the liver and small intestine was hybridized to plgR cDNA. Lane 1, C57BL/6 liver; lane 2, HIGA liver; lane 3, BALB/c liver; lane 4, BALB/c small intestine; lane 5, C57BL/6 small intestine; lane 6, HIGA small intestine. Mice were 48 wk old.

| **Table II. Age-related changes of IgA parameters** |
|-------------------|-------------------|-------------------|
|                  | BALB/c            | C57BL/6           | HIGA              |
| Serum IgA         | ↑                 | ↑                 | ↑                 |
| IgA-PCA in LP     | →                 | →                 | →                 |
| IgA+ B cells in Peyer’s patch | → | →                 | →                 |
| Peritoneal B-1 cells | → | →                 | →                 |
| Fecal IgA         | →                 | →                 | →                 |
| IgA deposition in the kidney | → | →                 | →                 |

* ↑, increased; ↑↑, markedly increased; ↓, decreased; →, unchanged.

Acknowledgments

We thank Dr. H. Hiai for his advise and comments on cytological analysis. We thank Y. Kobayashi, T. Tanuchi, and M. Tanaka for their technical assistance and M. Yamaguchi for her assistance in preparation of the manuscript.

References