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Expression of complement receptor type 1 and type 2 in murine AIDS

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Complement receptor type 1 (CR1), and type 2 (CR2) are expressed on the surface of B-cells and follicular dendritic cells (FDCs) in lymphoid follicles of mice. The importance of CR1 and CR2 in humoral immune response is well documented. Retrovirus-induced immunodeficiency syndrome, murine AIDS (MAIDS), results in abnormal humoral immune responses, destruction of lymphoid structures, and loss of FDC functions, namely trapping of antigens (Ags) and their retention on the cell surface. We investigated the expression of CR1 and CR2 in the spleen and lymph nodes of mice withMAIDS. Flow cytometry and immunohistochemistry revealed the existence of a correlation between the decrease in the expression of CR1 and CR2 by B-cells and the progression of the disease. However, expression of CR1 and CR2 by FDCs was maintained in the later stage of the disease in which lymphoid follicles were destroyed and the ability of FDCs to trap and retain Ag was severely impaired or lost. Moreover, FDCs expressing CR1 and CR2 but not FDCs-specific Ag (FDC-M1 antigen) proliferated in destroyed lymphoid structures. Although the ability of FDCs to trap and retain Ag *in vivo* was impaired, FDCs trapped immune complexes supplemented with complements in cryostat sections. In addition, FDCs proliferating in MAIDS displayed the same ultrastructural characteristic as normal FDCs, and expressed CD23. We conclude that decreased CR1 and CR2 expression in B-cells and continuous CR1 and CR2 expression in dysfunctional FDCs is important in the pathogenesis of MAIDS.
Key words complement receptors, murine AIDS, follicular dendritic cells, B-cells

INTRODUCTION

Murine complement receptor (CR)-1 and CR2 are products of an alternatively spliced gene, designated by *Cr2* and are expressed primarily on the surface of B-cells and follicular dendritic cells (FDCs)[1]. The importance of CR1 and CR2 in humoral immune response is well-documented[1]. For instance, $Cr2^{-/-}$ mice have an impaired humoral immune response to T-dependent antigen (Ag)[2-4]. In the germinal centers of lymphoid follicles (LFs), B-cell CRs associate with complement components of immune complexes (ICs) present on the surface of FDCs, and binding of antigens to B-cell Ag receptors occurs on the surface of FDCs[5]. These events may be important for the proliferation of B-cells, and their differentiation into memory cells and precursors of plasma cells[6]. FDCs retain Ag in the form of ICs for a long period of time[7]. Although the precise mechanism by which Ag is trapped and retained on the surface of FDCs has not been fully elucidated, it is apparent that CR1 and CR2 play important roles in these functions[7]. Loss of follicular IC trapping due to a lack of expression of CR1 and CR2 by FDCs leads to an impairment of Ag-specific immune response[8]. The roles of Ag retained on the surface of FDCs include the maintenance of memory B-cells, prolonged antibody (Ab) production[7], and affinity maturation of B-cells in the germinal center[6]. $Cr2^{-/-}$ mice display accelerated loss of serum Ab and long-lived Ab-forming cells[4].

Murine AIDS (MAIDS) induced by LP-BM5 murine leukemia virus (MuLV), is an useful model for investigating retrovirus-induced immunological abnormalities[9,10]. In MAIDS, abnormality in the humoral immune response and B-cell function is similar to HIV infection and includes impaired specific Ab response, polyclonal B-cell activation, hyperimmunoglobulinemia and auto-Ab production[9,10]. The levels of serum-specific Ab levels fall rapidly in MAIDS mice[11]. Changes have been identified

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in several molecules on the surface of lymphocytes in MAIDS, that are important for normal immune function[12]. Although HIV infection decreases the expression of B-cell CR2[13], the effect of MAIDS on the expression of B-cell CR not known.

The trapping and retention of Ag by FDCs are impaired during the early stageof MAIDS[11,14]. In the later stages, a destruction of lymphoid tissue and a loss of FDCs become apparent[14]. The destruction of FDCs is also a prominent feature of HIV infection[15]. Although the immunological mechanism leading to dysfunction and destruction of FDCs in MAIDS remains unknown, it is clear that FDC dysfunction is an important factor in the establishment of immunodeficiency[11,14,16]. We previously reported the presence of CR^+ FDCs in disorganized lymphoid tissues of advanced MAIDS[17]. However, the characteristics of these FDCs remain unknown. Therefore, we investigated the effect of MAIDS on the expression of CR in the spleen and the lymph nodes (LNs).

Materials and Methods

Preparation of LP-BM5 MuLV

LB-BM5 MuLV pools were produced from chronically infected SC-1 cells, clone G6, by cocultivation with non-infected SC-1 cells as described previously[18]. LP-BM5 is a mixture of infectious B-tropic ecotropic and mink cell focus-inducing viruses containing an etiologic replication-defective genome termed BM5def[18]. The titer of ecotropic virus in the pool was determined in SC-1 cells by XC plaque assay[19]. The virus pools contained $10^{5.2}$ to $10^{5.6}$ XC plaque-forming units per ml.

Mice and tissue preparation

C57BL/6 mice were purchased from Japan SLC (Shizuoka, Japan). Female mice at 4 to 5 week of age were inoculated intraperitoneally with 0.2 ml of LP-BM5 MuLV. The mice were maintained under specific pathogen-free conditions. At pre-determined times after infection, the mice were heavily anesthetized, and the spleen and the systemic LNs were removed. A large part of the spleen was used for flow cytometric analysis. The remaining of the spleen and the systemic LNs were processed for frozen sections. Other groups of mice were heavily anesthetized and perfused intracardially with 50 ml of pre-warmed Ringer's solution, followed by 50ml of 4% periodate-lysin paraformaldehyde solution. The excised spleen and LNs were further incubated in the same fixative for 6 h at 4°C.

Antibodies and flow cytometry

Monoclonal Ab (mAb) used for flow cytometry and immunohistochemistry were anti-CD45R/B220 mAb (CD45R, Ly-5), anti-CR2/1 mAb (CD21/35, 7G6), anti-CR1 mAb (CD35, 8C11), anti-CD23 mAb (B3B4), anti-FcγRII/III mAb (2.4G2), anti-intercellular adhesion molecule (ICAM)-1 mAb (CD54) (all from PharMingen, San Diego, CA). Anti-murine FDC mAb (FDC-M1[20]) was kindly supplied by Dr. M. Kosco-Vilbois, (Glaxo Wellcome Geneva, Switzerland). Because CR1 and CR2 are products of an alternatively spliced gene, anti-CR2 mAb is not available[1]. Peroxidase-conjugated, affinity purified $F(ab')_2$ fragments of mouse IgG that react specifically with rat IgG heavy and light chains (Jackson ImmunoResearch Lab., West Grove, PA) were used as secondary Ab. FITC-conjugated anti-CR2/1 (7G6) mAb and FITC-conjugated anti-CD45R/B220 mAb were used for flow cytometry. PE-conjugated strept-avidin was used as second step reagent for biotinylated mAbs.

Immunohistochemistry for light microscopy

Frozen tissues were sectioned (4μm-thickness) on a cryostat, fixed in acetone for 10 min, and fixed in chloroform for 10 min at room temperature. In some sections, endogenous peroxidase activity was blocked by incubation with 0.3% H_2O_2 in distilled water for 30 min at room temperature. Sections were incubated overnight at 4°C with optimally diluted mAbs and for 1 h at room temperature with optimally diluted, peroxidase-conjugated secondary Ab. Peroxidase activity was detected in the presence of 0.03% 3, 3'-diaminobenzidine (Dojin Chemical, Tokyo, Japan) and 0.01% H_2O_2 in 0.05 M Tris-HCl buffer, pH7.5.

IC trapping in cryostat sections

IC trapping assay in cryostat sections was

performed according to the procedure reported by Yoshida et al[21]. Ten μm thick cryostat sections were incubated at 4°C with mouse peroxidase-anti-peroxidase IgG (DAKO, Denmark) diluted to 1 : 20 in phosphate buffered saline (PBS) containing either no serum or 20% mouse serum, which was used as source of complements. After the sections were rinsed in PBS, peroxidase activity in the sections was visualized as described above. Incubation with horseradish peroxidase solution was performed as a control. Blocking experiments were performed by addition of 25 μg/ml of anti-CR2/1 mAb during the above-mentioned incubation.

Immunoelectron microscopy

Fifty-micron sections were prepared from perfusion-fixed tissues with an Oxford vibratome. To inhibit non-specific binding of mAb, sections were incubated overnight at 4°C in 5% bovine serum albumin in PBS. Sections were then incubated overnight at 4°C in optimally diluted mAb. After an overnight wash in PBS, the sections were incubated overnight at 4°C in diluted peroxidase-conjugated secondary Ab. After an overnight wash in PBS, the sections were incubated with 0.1% 3, 3'-diaminobenzidine in 0.05 M Tris-HCl, pH 7.5 for 1 h at room temperature. The incubation was continued in the presence of H_2O_2 for 30 min. The sections were mounted on glass slides and examined with a light microscope to select the appropriate areas. The selected areas were trimmed and post-fixed with 2% OsO4 in 0.1 M cacodylate buffer, pH 7.0, for 90 min, dehydrated in a gradual concentration series of ethanol solutions, and embedded in Epon 812 on blank epoxy stubs for cutting with an ultramicrotome. Unstained ultrathin sections were examined at 60KV with a Hitachi HU-12A electron microscope.

Results

Relation between the expression of B-cells CR and the progression of MAIDS

B cells expressing CRs were detected by flow cytometry (Fig. 1). In normal spleen, about half of the CD45R/B220$^+$ B-cells expressed CR1 and over 90% of the B-cells were positive for CR2/1. Similar results were obtained from splenic

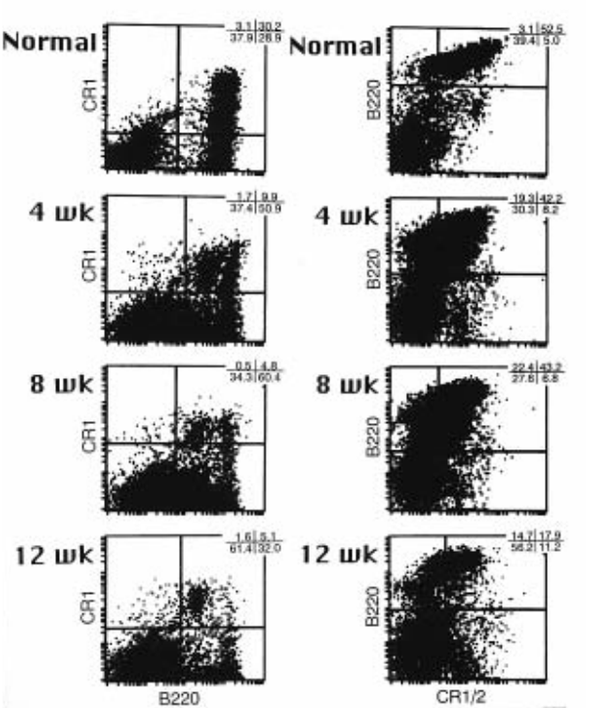

Fig. 1. Representative flow cytometric analysis of CR1 and CR1/CR2 in spleen cells isolated from non-infected mice or mice infected with LP-BM5 MuLV, 4, 8 or 12 weeks before observation. Splenic lymphocytes were stained with FITC-conjugated anti-CR2/CR1 mAb (7G6), biotinylated anti-CD45RO/B220 mAb, FITC-conjugated anti-CD45R/B220 mAb, and biotinylated anti-CR1 mAb as described in Materials and Methods. The percentages of respective cell types over total lymphocytes are shown.

lymphocytes from mice, 2 weeks after LP-BM5 infection (data not shown). CR$^+$ B-cells decreased dramatically in mice, 4 weeks after infection. About 15% of the B-cells were CR1$^+$ and 66% of the B-cells were CR21$^+$, 4 weeks after infection. Although the relative number of B-cells decreased gradually, the ratio of CR1$^+$ B-cells to total B-cells remained constant through 12 weeks after infection. The ratio of CR2/1$^+$ B-cells to total B-cells decreased approximately by 50%, 12 weeks after infection.

expression of FDC CR in destroyed lymphoid structures

Expression of CR in spleen (Fig. 2 and 4) and LNs (Fig. 3) was examined by immunohistochemistry. In non-infected mice, FDC CR2/1

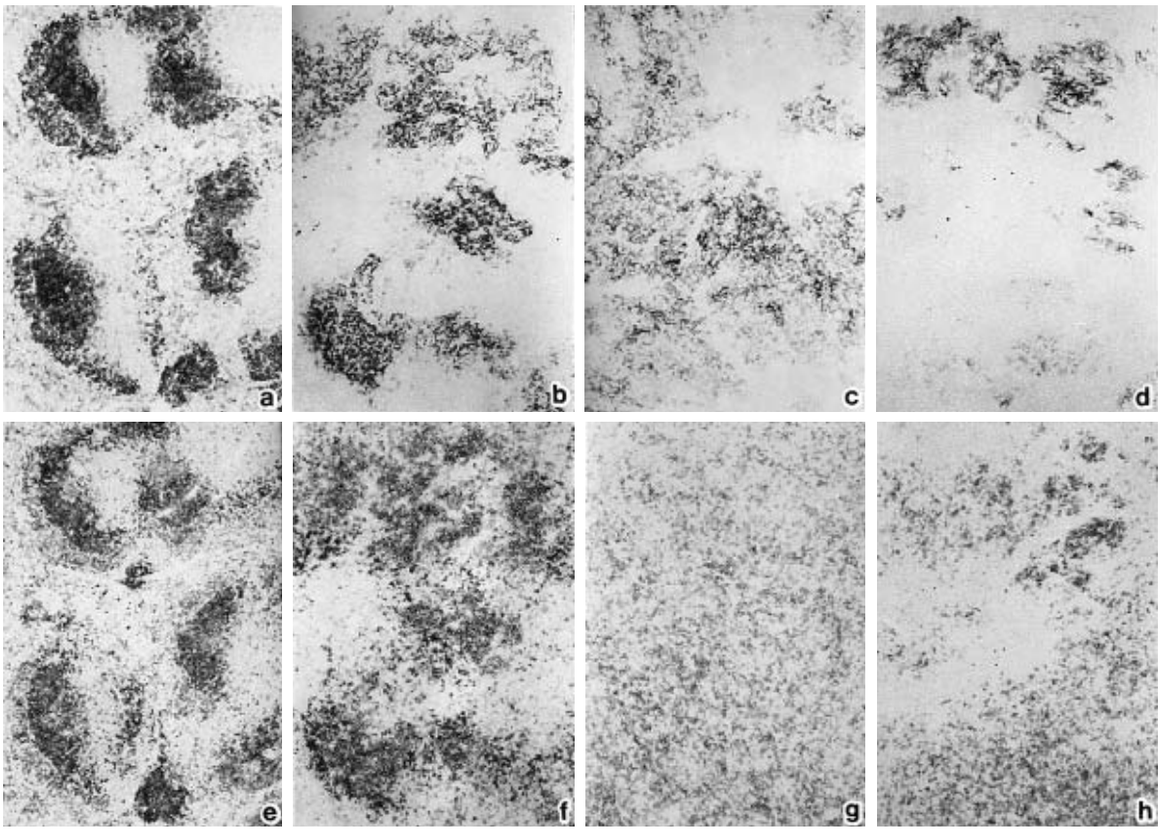

Fig. 2. Immunohistochemistry of CR1/2 (a, b, c and d) and CD45R/B220 (e, f, g and h). Splenic sections of non-infected mice (a and e : serial sections) and mice 4 (b and f : serial sections), 8 (c and g : serial sections), or 12 weeks (d and h : serial sections) after infection with LP-BM5 were stained with anti-CR2/1 mAb and anti-CD45R mAb (CD45R/B220) (magnification×45).

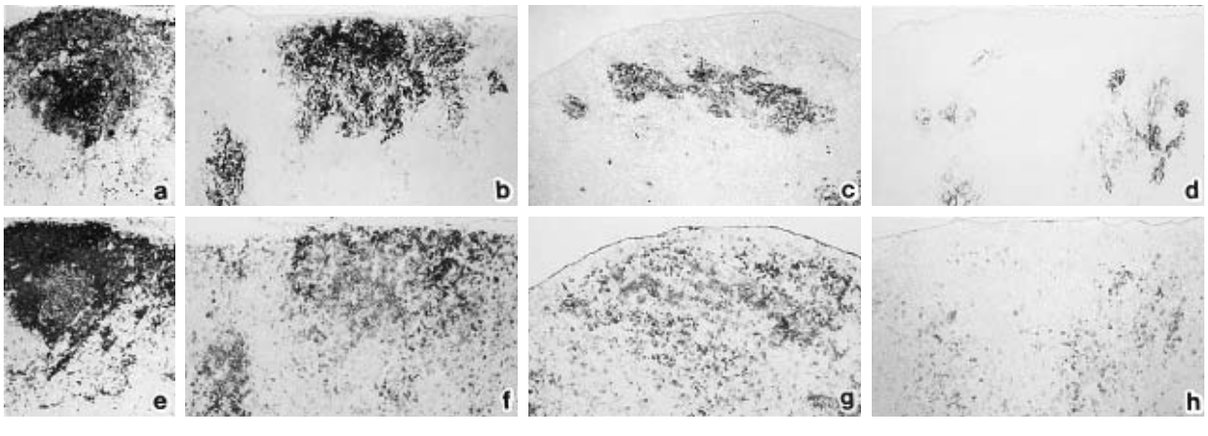

Fig. 3. Immunohistochemistry of MAIDS LNs of CR1/2 (a, b, c and d) and CD45R/B220 (e, f, g and h). LNs of non-infected mice (a and e : serial sections) and mice 4 (b and f : serial sections), 8 (c and g : serial sections), and 12 weeks (d and h : serial sections) after infection with LP-BM5 were stained with anti-CR2/1 mAb and anti-CD45R/B220 mAb (magnification×48).

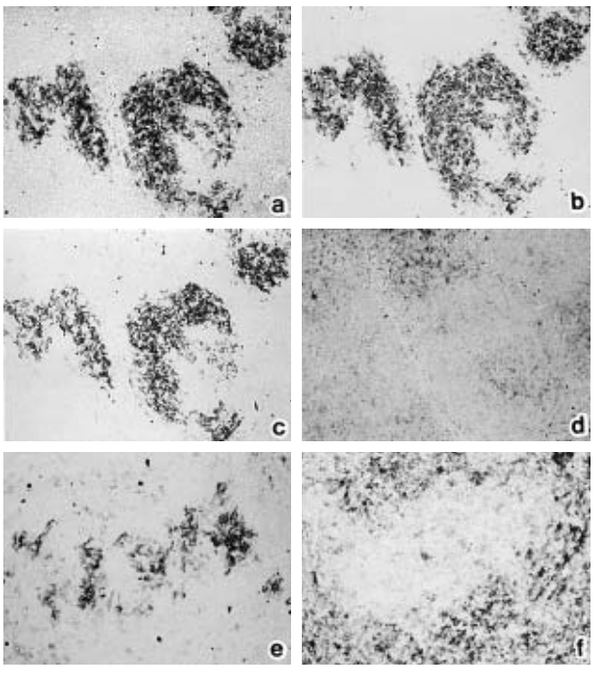

Fig. 4. IC trapping in cryostat sections. Mouse peroxidase-anti-peroxidase IC with (c and e) or without (d and f) fresh serum as a source of complements was applied to splenic sections from MAIDS mice 4 (a through d) and 8 weeks (e and f) after infection. The serial sections from mice 4 weeks after LP-BM5 infection were stained with anti-CR2/1 mAb (a) and anti-CR1 mAb (b) (magnification× 45).

expression appeared as a lacy network, and the expression of B-cell CR2/1 was equivalent to previously reported results[22]. Analysis of serial sections of spleen and LNs revealed that the distribution of CR2/1$^+$ lymphocytes and CD45R/B220$^+$ cells were almost the same. The pattern of CR expression in hyperplastic LFs of spleen and LNs 2 to 3 weeks after LP-BM5 infection was similar to the pattern displayed in normal LFs.

In MAIDS, the architectural deterioration of LFs becomes apparent 4 weeks after infection[14]. It has been reported that there were only fragmented FDC-M1$^+$ FDCs in LNs and no FDC-M1$^+$ FDC in spleen 4 weeks after infection[14]. CR2/1 immunoreactivity revealed the presence of a well-developed lacy network of FDCs in deteriorated LFs of spleen and of LNs 4 weeks after infection. A decrease of B-cells expressing CR2/1 was also apparent. It has been reported that eight weeks after infection, random intermingling of B-cells and T-cells, including a large number of T-cells with an unusual phenotype (Thy-1$^-$CD4$^+$), was identified in the white pulp of the spleen instead of the LF structure[17]. At this stage of the disease, scattered B-cells were visible, and only a small number of B-cells was positive for CR2/1. However, an ample and irregular network of CR2/1 was detected in the spleen. Although severely destroyed LFs and irregular networks of CR2/1$^+$ FDCs were also detected, CR2/1$^+$B-cells were hardly observed in LNs 8 weeks after infection. Twelve weeks after infection, the CR2/1 networks were still visible in the spleen, and some of these foci were associated with irregularly aggregated B-cells. A distinctive lacy pattern of FDC was detected in the LNs even 12 weeks after infection and these networks were accompanied by scattered B-cells. Similar staining patterns were detected with anti-CR1 mAb (Fig. 4). Networks of FDCs positive for CR2/1 and CR1$^+$ were negative for FDC-M1 in MAIDS mice 8 and 12 weeks after infection (data not shown).

IC trap assay for CR on the surface of dysfunctional FDCs

In the presence of complements, FDC CR1 and CR2 mediate *in vitro* IC trapping in frozen sections[21]. Four weeks after infection, IC trapping in the presence of complement was detected in the destroyed LFs of the spleen and LNs (Fig. 4). The trapping pattern was almost identical to the distribution of CR2/1 and CR1, 4 weeks after infection. IC trapping was still detected 8 weeks after infection. IC trapping was blocked by anti-CR2/1 mAb (7G6). Without supplementation of complements, IC trapping was not detected on the surface of FDCs, 4 weeks and 8 weeks after infection, although diffuse and faint trapping was observed in the rest of the specimen.

Characteristics of CR$^+$ FDC in destroyed lymphoid tissue

Since FDCs identified by the expression of CR did not display FDC-M1 Ag and were not localized in LFs, the authenticity of these putative, dysfunctional FDCs were examined by immunoelectron microscopy. Observation of the foci of CR$^+$ FDC proliferation revealed the presence of CR2/1$^+$ cytoplasmic processes between CR2/1$^-$ lymphocytes (Fig. 5). CR2/1$^+$ lymphocytes were rarely observed. CR2/1$^+$ cells

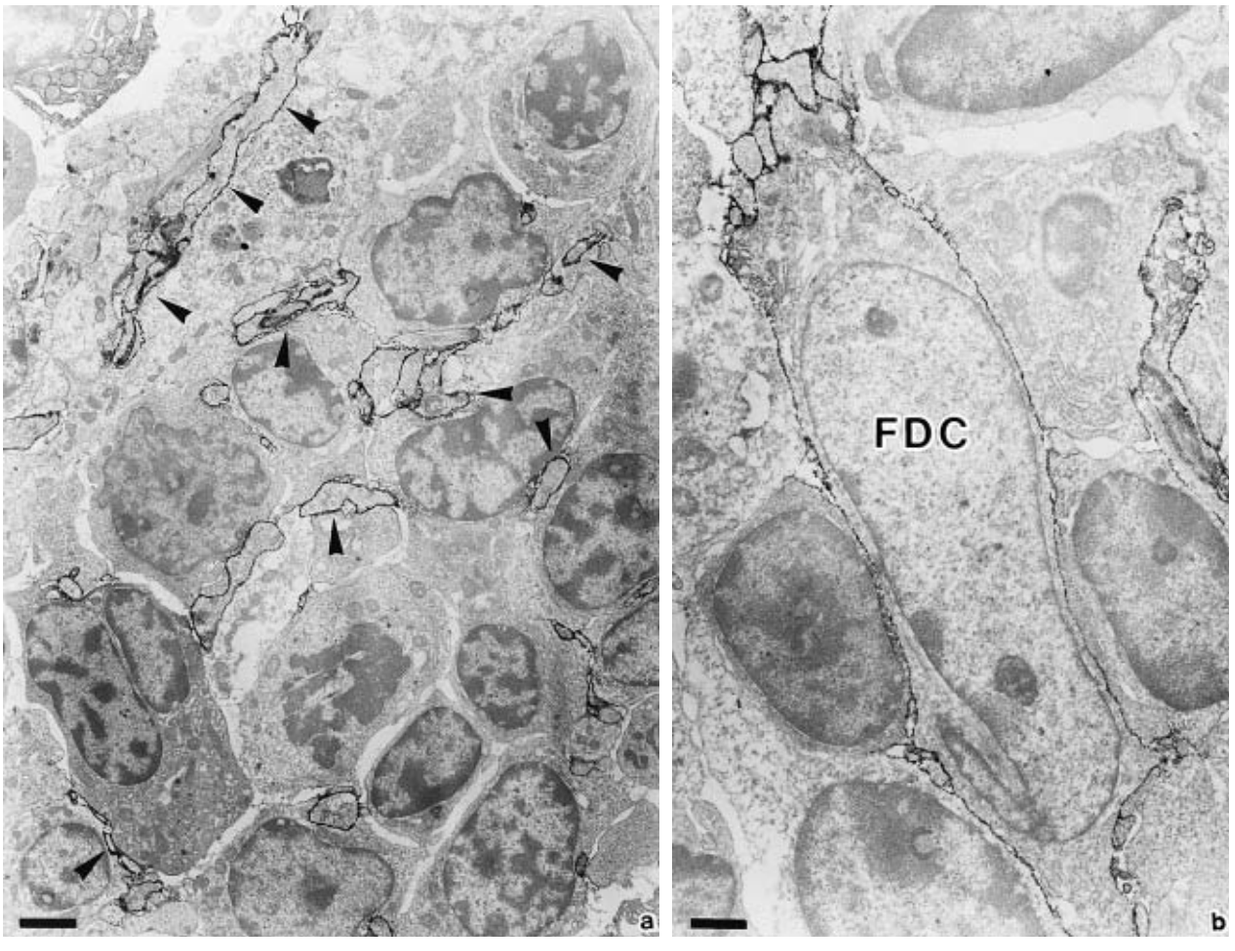

Fig. 5. Ultrastructure of CR2/1-immunoreacive splenic cells from MAIDS mice. Ultrathin sections from the spleen of MAIDS mouse 8 weeks after infection immunostained with CR2/1 mAb. Although no immunoreactivity is detected on the surface of lymphocytes, thin cytoplasmic processes between lymphocytes display positive CR2/1 immunoreactivity (arrow heads) (a ; magnification×4000, bar=2μm). CR2/1 positive FDC displays complex cytoplasm and an euchromatic nucleus (b, magnification×8000, bar=1μm)

Fig. 6. Immunohistochemical localization of CD23 (a), ICAM-1 (b) and FcγRII/III (c) in MAIDS mice 8 weeks after infection. Splenic sections were stained with anti-CD23 mAb (a), anti-CD54 mAb (b) and anti-FcγRII/III (2.4G2) mAb (c). (magnification×45)

had a large euchromatic nucleus and complex cytoplasmic processes (Fig. 5), which are ultrastructural characteristics of FDCs[7]. Multinucleated FDCs were hardly found.

Since murine FDCs also express CD23, CD54, and FcγRII/III[7,23], putative dysfunctional CR$^+$ FDCs localized in the destroyed white pulp of the spleen was examined immunohistochemically for the expression of these molecules (Fig. 6). In MAIDS mice, analysis of serial sections revealed that CR2/1$^+$ FDCs and CD23$^+$ cells had a similar distribution through the entire course of the disease. However, the expression of ICAM-1 (CD54), and FcγRII/III (detected by 2.4G2[24]) was weak and diffuse throughout the destroyed white pulp of the spleen. These staining patterns were different from those observed in LFs of uninfected mice, in which FDCs were clearly identified with these markers[23].

DISCUSSION

Reduction in the expression of CR on the surface of B-cells has been reported in MRL MpJ-*lpr*/*lpr* mice[25]. Abnormalities of humoral immunity between MAIDS and MRL MpJ-*lpr*/*lpr* mice are similar[26], including polyclonal B-cell activation, auto-Ab production, and impairment of specific Ab response. CR1 and CR2 are important for regulating autoimmunity and Ag-specific Ab response[1]. Interestingly, FDCs in MRL MpJ-*lpr*/*lpr* mice display expression of CR, impaired Ag retention and positive IC trapping capability in cryostat sections[27]. The similar FDC abnormalities found in both MAIDS mice and MRL MpJ-*lpr*/*lpr* mice underscore the importance of FDC dysfunction in a disorder of humoral immunity.

Here we demonstrated the presence of functional CR as indicated by their ability to trap IC in cryostat sections with the presence of complement. Dysfunction in FDCs of trapping and retention of *in vivo*-administered Ag becomes apparent in the early stage of MAIDS in which FDC expression of FcγRII/III is clearly present[14]. Therefore, the loss of long-term Ag retaining function in MAIDS is not likely to be due to the loss of expression of CR and/or FcγRII/III. Although CR and FcγR are thought to play central roles in Ag handling by FDCs, it is clear that a complex mechanism involving other molecules may contribute to Ag trapping *in vivo* and the long-term Ag-retaining function of FDCs. Tumor necrosis factor signaling is essential for maintaining IC on the surface of FDCs[28]. It is not known whether a tumor necrosis factor receptor-mediated signaling pathway is involved in defective FDC function in MAIDS mice. Further study is necessary to understanding the mechanism of FDC function.

In MAIDS, CR$^+$ cells proliferating without LF structure can be identified as FDCs despite the absence of FDC-M1 expression, because of their dendritic shape, expression of CR1, CR2, and CD23, and ultrastructural features. The lymphoid structure at a later stage of MAIDS is characterized by the intermingling of T- and B-cells with an unusual subset of T-cells, Thy-1$^-$ CD4$^+$[17]. Here, we confirmed that FDCs with impaired function is a major component of the deteriorated lymphoid structure. FDCs in MRL MpJ-*lpr*/*lpr* mice also display reduced expression of FDC-M1[27].

Although it is possible that dysfunctioning CR$^+$FDC-M1$^-$ FDCs may play an active role in the abnormal interaction of cells in MAIDS, further investigation is needed to determine a precise role for the dysfunctioning FDCs. Diffuse expression of ICAM-1, and FcγRII/III may also play a role in the abnormal interactions occurring between the cells of the disorganized lymphoid structures found in MAIDS.

Proliferation of FDCs without LFs or LF-like structures found in MAIDS is also observed in angioimmunoblastic T-cell lymphoma and Hodgkin's disease[29]. In both diseases, proliferation of FDCs is detected in lesions where intermingling occurs among tumor cells and non-neoplastic cells, which include T-cells, B-cells, plasma cells, and eosinophiles[29]. Although these diseases differ, the mechanism by which CR$^+$ FDCs proliferate may be similar.

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