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Development of follicular dendritic cells: A study using short-term bone marrow cell grafting in SCID mice

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Summary. To evaluate the cellular origin of follicular dendritic cells (FDC) in lymphoid follicles (LFs), severe combined immunodeficient (SCID) mice (H-2^d) were grafted with 5-bromo-2'-deoxyuridine (BrdU)-incorporated bone marrow cells from CB-17 mice (H-2^d) and with non-BrdU-incorporated bone marrow cells from C3H mice (H-2^k) and Wistar rats (RT1^u). This procedure was followed by antigenic stimulation with horseradish peroxidase and related immune complex (mouse peroxidase anti-peroxidase) administration. Secondary LFs in the lymph nodes and spleen of the reconstructed SCID mice were examined morphologically and immunocytochemically. LFs reconstructed with CB-17 mouse bone marrow cells contained FDCs capable of trapping and/or retaining mouse peroxidase anti-peroxidase as immune complexes. Secondary LFs contained BrdU-incorporated germinal center lymphocytes but not non-lymphoid stromal cells. A cell grafting study in SCID mice using bone marrow cells from C3H mice and Wistar rats demonstrated that FDCs in reconstructed LFs exhibited a marker specific for the recipient but not for the donor. These data indicate that functionally active FDCs occur *de novo* in reconstructed LFs in SCID mice, and do not support the view that FDCs originate from bone marrow cells in short-term reconstructed LFs.

Key words: Follicular dendritic cells, Cellular origin, Bone marrow grafting, SCID mice

Introduction

B-cell associated dendritic cells, so-called follicular dendritic cells (FDCs) are found in non-neoplastic and neoplastic lymphoid follicles (LFs) (Imai and Yamakawa, 1996; Imai et al., 1998). FDcs are essential for generating antigen-specific memory B cells and plasmablasts (MacLennan et al., 1992), and have the following functions: 1) formation of a three-dimensional reticular structure within LFs by joining together through desmosome-like junctions and by adhesion to extracellular matrices expressing receptors for them (Imai and Yamakawa, 1996; Ogata et al., 1996); 2) trapping and retaining immune complexes (ICs) on their cytoplasmic extensions via Fc and complement receptors accompanied with activation of complement system and deposition of blood coagulation and fibrinolysis factors (Imai et al., 1986a; Yamakawa et al., 1991; Yamakawa and Imai, 1992; Kudo et al., 1992; Dijstra et al., 1994; Imai and Yamakawa, 1998; Sato et al., 1996; Liu et al., 1997; Sato and Dobashi, 1998); 3) presentation of trapped antigen to the B cells in germinal center (GC) (Schriever and Nadler, 1992; van Rooijen, 1993; Nossal, 1994); 4) modulation of GC B cell apoptosis (Schriever and Nadler, 1992; van Rooijen, 1993; Nossal, 1994); and 5) formation of FDC-lymphocyte clusters (Orui et al., 1997). The FDCs express some kinds of cytokine receptors (Yamada et al., 1997) and their unique function is retention of ICs.

There have been many reports describing the cellular origin of FDCs using a variety of methods, including electron microscopy, ontogenic studies, enzyme- and immuno-histochemistry, cell culture, bone marrow chimeras, and molecular biology (Heinen and Bosseloir, 1994). The data derived from these studies support two alternative hypotheses, namely that they originate either from mesenchymal cells (fibroblastic reticulum cells) or from bone marrow monocytes.

A homozygous mutation in the severe combined immunodeficient (SCID) mouse resulted in disruption of both B- and T-cell lymphoid development, resulting in low serum immunoglobulin levels and the absence of functional T cells (Bosma et al., 1983; Resta and Thompson, 1997). The intrinsic ability of SCID mice to support lymphoid development, however, is not impaired. Immune function in SCID mice can be restored fully after reconstitution with normal mouse bone marrow (Dorschkind et al., 1984). The success of homogeneic and xenogeneic engraftment into SCID mice has stimulated many investigators to use SCID mice as a model system to study various aspects of immune function both in the normal and diseased

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states (Surh and Sprent, 1991; Donjon et al., 1993; Hendrickson, 1993; Hoffmann-Fezer et al., 1993; Nonoyama et al., 1993; Malkovska et al., 1994; Schaible et al., 1994; Kelly et al., 1997; Picarella et al., 1997). Reports of bone marrow cell grafting studies using SCID mice have produced conflicting results (Imai et al., 1993; Kapasi et al., 1993; Yoshida et al., 1994).

In the present study, bone marrow cells obtained from mice and rats were grafted to SCID mice to investigate whether or not FDCs originate from bone marrow cells. After antigenic stimulation and administration of IC the short-term reconstructed LFs were analyzed morphologically and immunocytochemically.

Materials and methods

1. Animals

SCID mice (CB-17/*scid*/*scid*, H-2^d), CB-17 mice (CB-17/Icr$^{+/+}$, H-2^d), C3H mice (H-2^k), and Wistar rats (RT1^u), all males, 6 to 8 weeks old, male (Clea Japan, Inc., Shizuoka, Japan) were fed in a specific pathogen-free environment. Only "non-leaky" SCID mice with total serum immunoglobulin levels below 0.5 μg/ml were used in the experiments.

2. Bone marrow cells

Bone marrow cells obtained from the femora of CB-17 mice, C3H mice, and Wistar rats were suspended and adjusted to 10^7 to 10^8 cells/ml of RPMI medium 1640 (Life Technologies, Gaithersburg, MO). 0.1 ml of cell suspension was transplanted intravenously to SCID mice via a tail vein. In addition, 0.1 ml of 5-bromo-2'-deoxyuridine (BrdU; Sigma Chemical Company, St. Louis, MO) solution in a concentration of 10 mg/ml of saline was administered intraperitoneally to ten CB-17 mice. After 3 hrs CB-17 mouse bone marrow cells were collected and 10^6 to 10^7 cells injected into SCID mice.

3. Preimmunization

Preimmunization to stimulate development of GCs was performed by intraperitoneal and subcutaneous footpad injections with 10^5 sheep red blood cells (SRBC)/ml of saline.

4. Antigenic stimulation

SCID mice with and without cell grafting and CB-17 mice were stimulated with intraperitoneal and subcutaneous footpad injections with 1 ml and 0.1 ml of horseradish peroxidase (HRP) (1 mg/ml of saline) (Toyobo Company, Osaka, Japan), respectively. Ten days later the subjects were rechallenged with HRP in a similar manner. A further 10 to 15 days later mice were injected with 1 ml and 0.1 ml of peroxidase anti-peroxidase (PAP) (1 mg/ml of saline) (American Qualex International, La Mirada, CA) intraperitoneally and subcutaneously in the foodpads, respectively.

5. Tissue specimens

1, 6, 12, 24, and 48 hrs after PAP challenge anesthetized SCID mice with and without cell grafting and CB-17 mice were perfused with 100 ml of 4% paraformaldehyde, and the popliteal lymph nodes and spleen removed and refixed with more 4% paraformaldehyde or B5 for 6 hrs at 4 °C. A portion of the paraformaldehyde-fixed tissues was treated in graded sucrose-0.01M phosphate-buffered saline, pH 7.4, embedded into Tissue-Tek II OCT compound (Miles Inc., Elkhart, IN) in acetone cooled by dry ice, and stored at -80 °C until cryostat sectioning for immunohistochemistry. The remaining paraformaldehyde-fixed specimens were cut into 50-100 μm-thick sections using a DTK-1000 microslicer (Dosaka EM, Kyoto, Japan). Sections were used for immunocytochemistry and electron microscopy for HRP localization. B5-fixed tissues were embedded in paraffin, sectioned, and used for immunohistochemistry for BrdU.

6. HRP localization

Vibratome sections were incubated in 3,3'-diaminobenzidine (DAB; Dojin Chemicals, Kumamoto, Japan) and then H_2O_2, and refixed in 1.25% glutaraldehyde and 1% osmium tetroxide. Sections were then processed in the usual way, by dehydration in graded alcohol. Propylene oxide sections were embedded in epon, thinly sectioned, and observed under an electron microscope (EM109; Zeiss, Germany).

7. Immunochemistry

Immunochemistry was performed using the avidin-biotinylated peroxidase method. Cryostat and vibratome sections were immunostained with biotinylated anti-mouse H-$2K^d$ and H-$2K^k$ (Meiji Nyugyo, Tokyo, Japan), rat monoclonal antibody against mouse FDC (FDC-M1) (gift of Drs. K. Maeda and M.H. Kosco-Vilbois in the First Department of Pathology, Yamagata University School of Medicine, and the Basel Institute for Immunology, Switzerland, respectively) (Kosco et al., 1992). After DNA denaturation with 2N HCl for 15 min biotinylated mouse anti-BrdU antibody (Becton-Dickinson, Bedford, MA) was applied to paraffin sections to detect BrdU-incorporated cells in reconstructed LFs. Avidin DH-biotinylated HRP H (Vectastain Elite ABC kit; Funakoshi, Tokyo, Japan) was applied to sections and a DAB reaction was performed. Sections were counterstained with hematoxylin, toluidine blue or methylgreen.

8. Peanut agglutinin (PNA) stain

To detect GC cells HRP-labeled peanut agglutinin (PNA; Sigma Chemical Company, St. Louis, MO)

staining was performed (Kapasi et al., 1993). After the DAB reaction sections were counterstained with hematoxylin.

9. Experimental design

1) Cell grafting into SCID mice by CB-17 mouse bone marrow cells

One ml of BrdU was administrated intraperitoneally to ten CB-17 mice. An identical volume of saline was given in the same way to a further ten control mice. After 3 hrs a bone marrow cell suspension was prepared and 0.1 ml of 10^7 to 10^8 cells/ml was injected into the tail vein of SCID mice. Two weeks later 10^5 SRBC were given by intraperitoneal and subcutaneous footpad injections into SCID mice, and HRP was simultaneously administrated at the same sites. Ten and twenty days later HRP and mouse PAP were injected in the same way. Sequentially after PAP challenge, the popliteal lymph nodes and spleen of SCID mice were excised. Control SCID mice were injected with the same volume of saline in place of HRP and PAP.

As further controls five SCID mice and four CB-17 mice were given intraperitoneal and subcutaneous footpad injections of SRBC and HRP. Ten days later HRP immunization was repeated in the same way. After a further ten days mouse PAP was injected in the same way. After the PAP challenge popliteal lymph nodes and spleen were sequentially removed.

2) Cell grafting into SCID mice by C3H mouse and Wistar rat bone marrow cells

Bone marrow cells obtained from C3H mice and Wistar rats were injected into the tail vein of five SCID mice. Three to four weeks later SRBCs were injected intraperitoneally and subcutaneously into the footpads. Ten to fifteen days later the popliteal lymph nodes and the spleen of SCID mice were excised.

Results

1. LF formation in SCID mice reconstructed with CB-17 mouse bone marrow cells

Secondary LFs of varying sizes were found in the popliteal lymph nodes and spleen of SCID mice (H-2d) reconstructed by CB-17 mouse (H-2^d) bone marrow cells (Fig. 1a,b). A lymph node or spleen generally contained several LFs. The GC was localized using PNA staining.

BrdU was detected in the nuclei of lymphocytes but not in the FDCs in GCs (Fig. 1c). Neither GC lymphocytes nor FDCs immunoreacted for BrdU in SCID mice reconstructed with non-BrdU incorporated CB-17 mouse bone marrow cells. In addition, SCID mice unstimulated by HRP followed by mouse PAP administration did not show distinct GC formation.

Electron microscopic observation of the GCs of reconstructed SCID mice 30 min after IC (mouse PAP) administration revealed that PAP was distributed diffusely on the surface of a large number of cells including GC lymphocytes and FDCs (Fig. 1d). 1 hr after PAP administration the amounts of PAP on the surface of lymphocytes gradually fell, until by 6 hrs most of the PAP was distributed on the surface of FDCs, and by 12 hrs PAP was largely restricted to the surface of FDCs (Fig. 1e). FDCs in reconstructed SCID mice were irregular, often with more than two nuclei exhibiting peripherally condensed chromatin. Rough endoplasmic reticulum was sparse and there were few lysosomes.

2. LF formation in SCID mice reconstructed with C3H mouse bone marrow cells

SCID mice (H-2^d) were grafted with bone marrow cells of C3H mice (H-2^k) (Fig. 2a). As with CB-17 mouse bone marrow cells secondary LFs contained PNA-positive GCs (Fig. 2b). Immunostains revealed that GC lymphocytes in reconstructed SCID mice were positive for H-2^k but not for H-2^d, while non-lymphoid stromal cells exhibiting many long cytoplasmic extensions were positive for H-2^d but not for H-2^k (Fig. 2c and 2d).

3. LF formation in SCID mice reconstructed with Wistar rat bone marrow cells

As in the other two experiments distinct PNA-positive GCs were detected. Immunostain for mouse FDCs with FDC-M1 demonstrated that reconstituted GCs contained recipient-derived FDCs (Fig. 3).

4. Controls

1) Antigenic stimulation in CB-17 mice

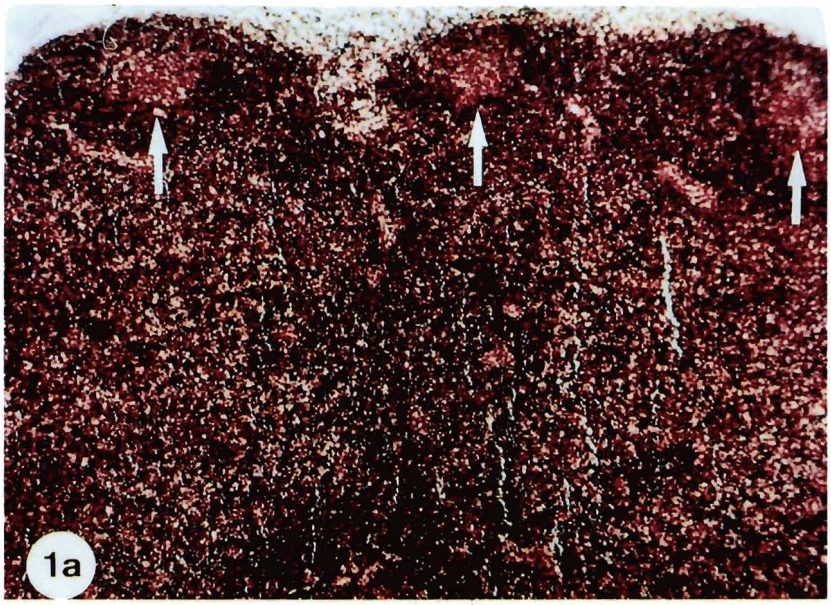
Stimulation with SRBCs induced primary and secondary LFs with distinctive GCs in lymph nodes and spleen. GCs in CB-17 mice were, in general, larger and in greater numbers than those in reconstructed SCID mice. FDCs in these LFs were shown to trap and retain ICs (Fig. 4). There was no major difference in cellular composition of the GCs or the ability to trap and retain ICs between reconstructed SCID mice and CB-17 mice.

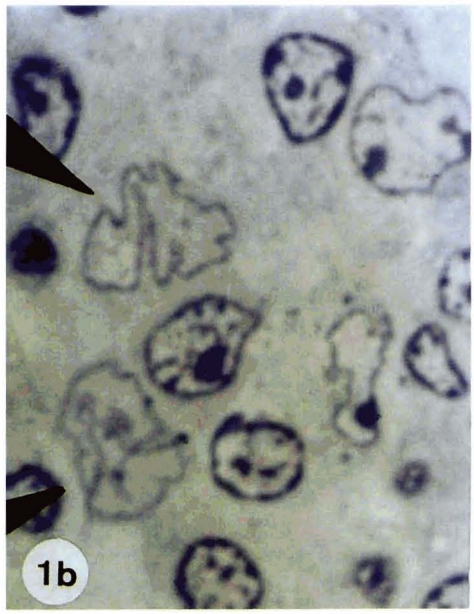
2) Antigenic stimulation in non-grafted SCID mice

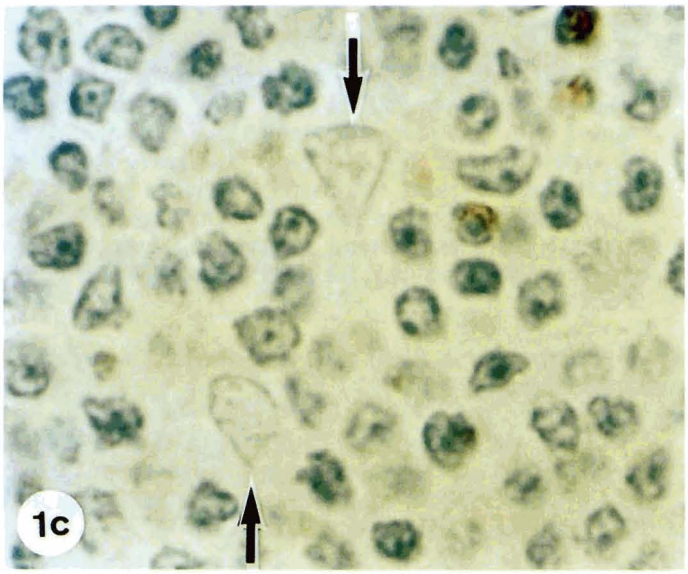
SRBC stimulation followed by PAP administration did not induce either GC formation or LFs that trapped ICs (Fig. 5).

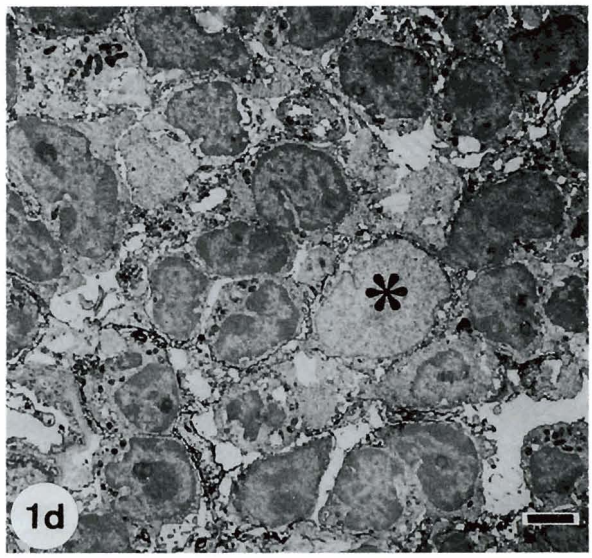
Discussion

Several reports have been published on the origin of FDCs using the techniques of cell grafting and tissue









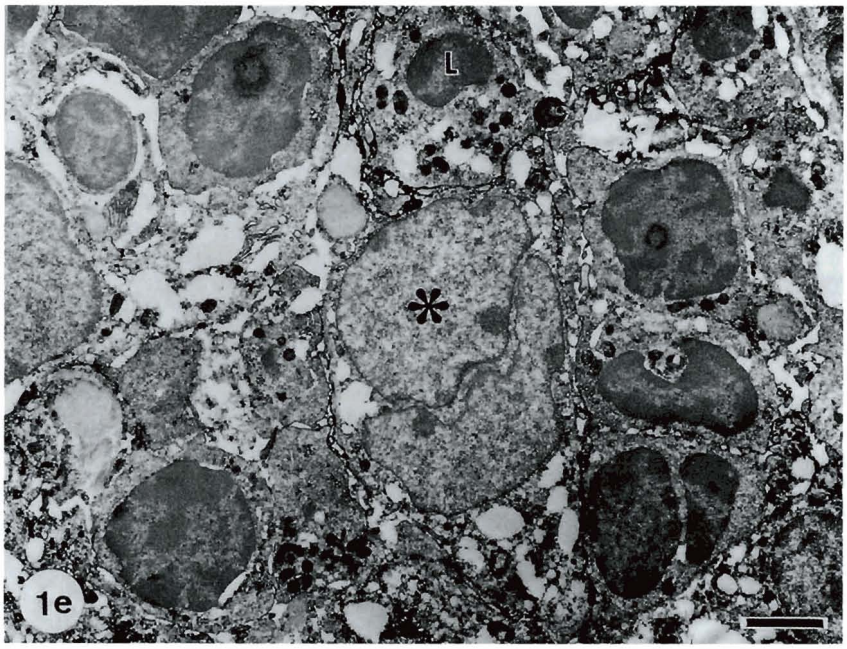


Fig. 1. Secondary lymphoid follicles in popliteal lymph node of SCID mice reconstructed with bone marrow cells of CB-17 mouse. **a.** Popliteal lymph node ten days after antigenic stimulation. Three small but distinct secondary lymphoid follicles are seen (arrows). Paracortical hyperplasia is also present. HE stain, x 40. **b.** Popliteal lymph node ten days after antigenic stimulation. High power view of follicular dendritic cells (arrows) with irregular nuclear contour in secondary lymphoid follicles (epon section). Toluidine blue stain, x 720. **c.** 5-bromo-2'-deoxyuridine immunostain, in a popliteal lymph node ten days after antigenic stimulation. The nuclei of a few germinal center lymphocytes but not follicular dendritic cell-like cells (arrows) are labeled. Counterstained with methylgreen, x 360. **d.** Popliteal lymph node one hour after peroxidase anti-peroxidase (PAP) administration. PAP is found in the intercellular space and on the cell surface of many cells including follicular dendritic cells (asterisk). x 5,000; Bar: 1 μm. **e.** Popliteal lymph node 24 hours after administration of PAP. PAP is found only on the cell surface of a binucleated follicular dendritic cell (asterisk) embracing a lymphocyte (L) with cytoplasmic extension. x 8,200; Bar: 1 μm.

implantation. Humphrey et al. (1984) performed a bone marrow chimerical study using CBA/B10 F1 mice and concluded that FDCs do not have their origin in the bone marrow. Results of studies using splenic implantation (Imazeki et al., 1992) concluded that mouse splenic FDCs are stationary and do not recirculate. Recent studies using SCID mice have yielded conflicting results. Those of Imai et al. (1993) and Yoshida et al. (1993, 1994, 1995) have not suggested a bone marrow origin, but Kapasi et al. (1993) speculated that FDCs are blood-borne antigen transporting cells (Szakal et al., 1988) and indicated that B-T cell collaboration and the factors these cells produce are essential for FDC development. Yoshida et al. (1994, 1995) observed splenic primary LF reconstructed in SCID mice. In the present study lymph node and splenic secondary LFs occurred after antigenic stimulation in SCID mice reconstructed by homogeneic and xenogeneic bone marrow cells were examined.

In the present control study antigenic stimulation failed to induce GC formation in non-reconstructed SCID mice. However, the same stimulation induced GC

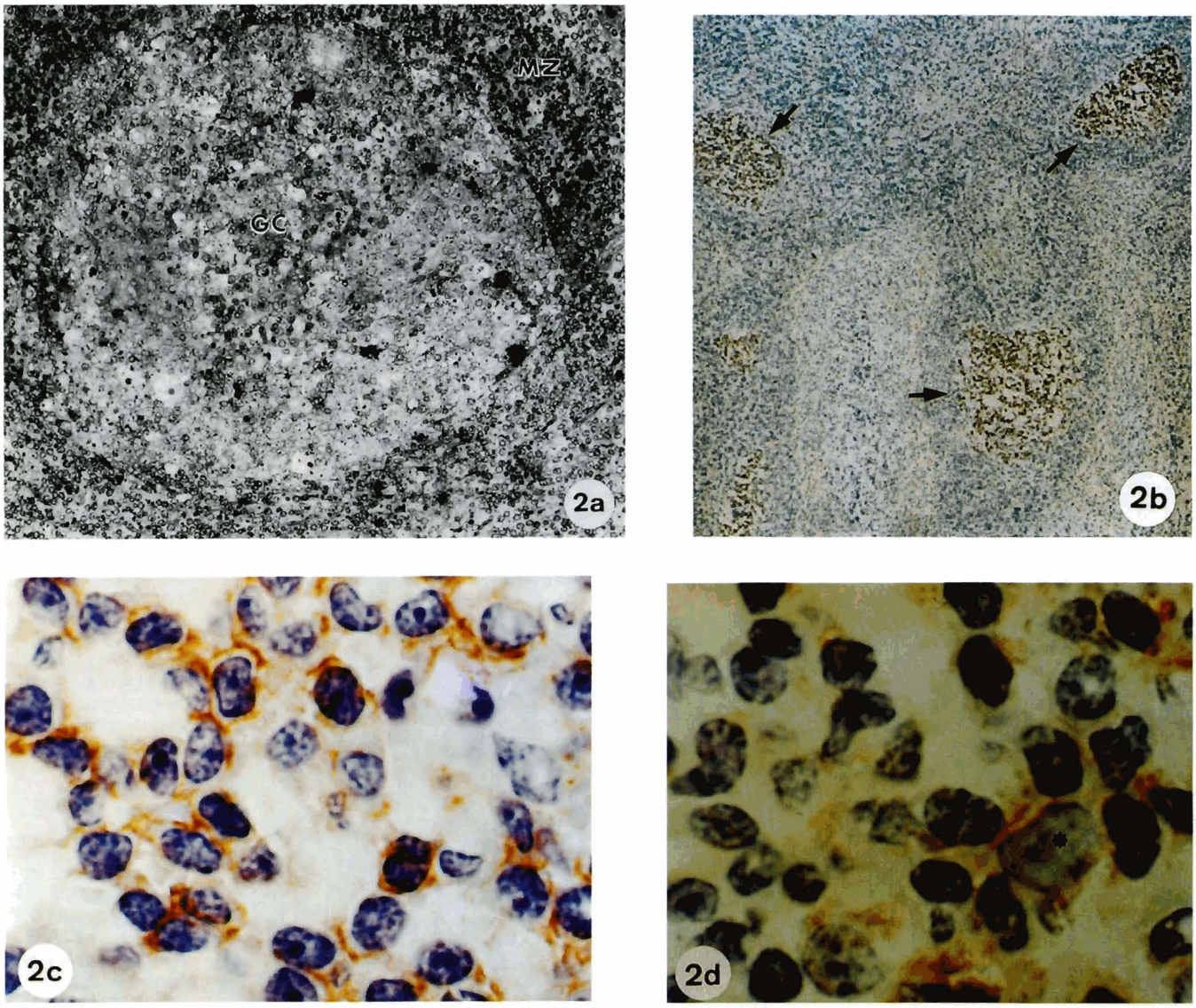


Fig. 2. Secondary lymphoid follicles of SCID mice reconstructed with bone marrow cells of C3H mouse. **a.** Like a conventional germinal center, the reconstructed secondary lymphoid follicle also comprises a germinal center (GC) and mantle zone (MZ). Epon section stained with toluidine blue, x 180. **b.** Peanut agglutinin stain in the splenic germinal center (arrows). Counterstained with methylgreen, x 20. **c.** Immunostain of H-2Kk in splenic germinal center, demonstrating that almost all GC lymphocytes are positive. However, no distinct immunoreaction is seen on follicular dendritic cells. Counterstained with hematoxylin, x 600. **d.** Immunostain of H-2Kd in splenic germinal center, demonstrating positive immunoreaction on follicular dendritic cell-like cell (asterisk). There is no distinct cell surface immunoreaction on lymphocytes. Counterstained with hematoxylin, x 600

formation in SCID mice reconstructed with bone marrow cells obtained from CB-17 mice, C3H mice, and Wistar rats, suggesting that normally functioning bone marrow cells including lymphocytes are essential for LF formation. The present electron microscopic study clearly demonstrated trapping and retaining of ICs by FDCs within secondary LFs. In the early phase (30-60 min) after IC (mouse PAP) administration it distributed diffusely on the surface of GC lymphocytes and FDCs. At 6 hrs most of the PAP localized on the surface of FDCs. Although it is difficult to make a clear distinction between IC-trapping and retaining, we suggest that PAP localization 24 hrs after administration indicates IC retention. Imai and Yamakawa (1996) and Imai et al. (1998) have reported that FDCs with a marked labyrinth-like structure and microvilli are widely distributed in the follicular light zone. The present ultrastructural observation confirmed the presence of similar FDCs in the follicular light zone. The nuclei of some GC lymphocytes incorporated BrdU, but we have never noted the same phenomenon in the nuclei of FDCs. The FDCs have very slight proliferative activity (Sato and Dobashi, 1996).

GC lymphocytes in SCID mice reconstructed with C3H mouse bone marrow cells were positive for H-2^k, a marker of C3H mouse cell origin, but not with H-2^k, a marker of SCID mouse cell origin. On the other hand, non-lymphoid stromal cells were H-2^k-positive and H-

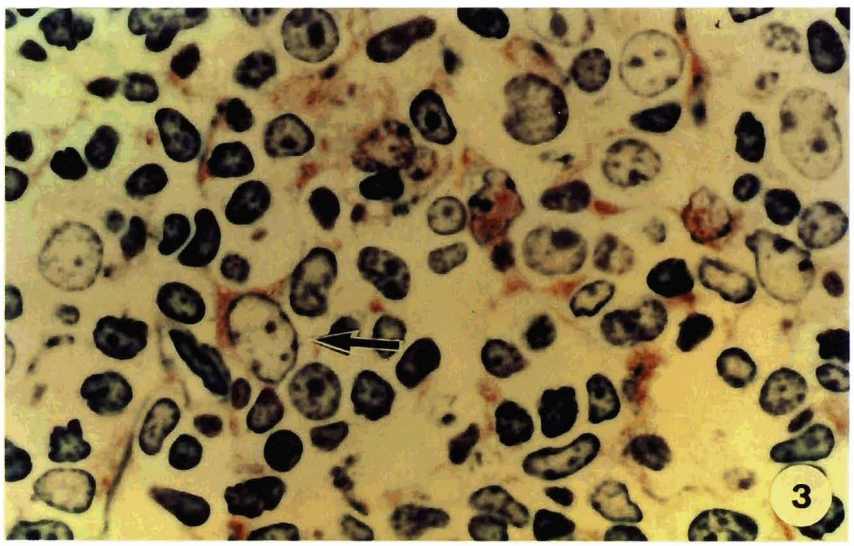


Fig. 3. Immunostain for FDC-M1 in splenic germinal center of SCID mice reconstructed with bone marrow cells of Wistar rat. Long cytoplasmic extension of follicular dendritic cell (arrow) shows a positive reaction. Epon-embedded section, counterstained with toluidine blue. x 750

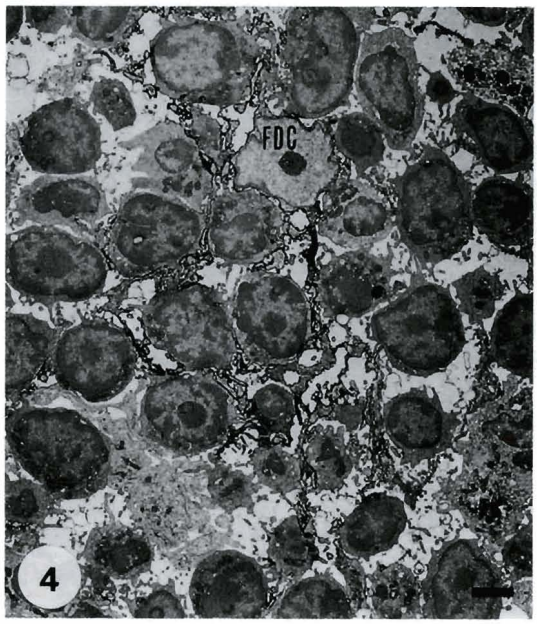


Fig. 4. Electron micrograph demonstrating the localization of peroxidase anti-peroxidase (PAP) in the splenic germinal center after 24 hours. The bulk of the PAP localizes to the follicular dendritic cell (FDC) surface, especially along the long cytoplasmic extensions. x 2,500; Bar: 2 μm.

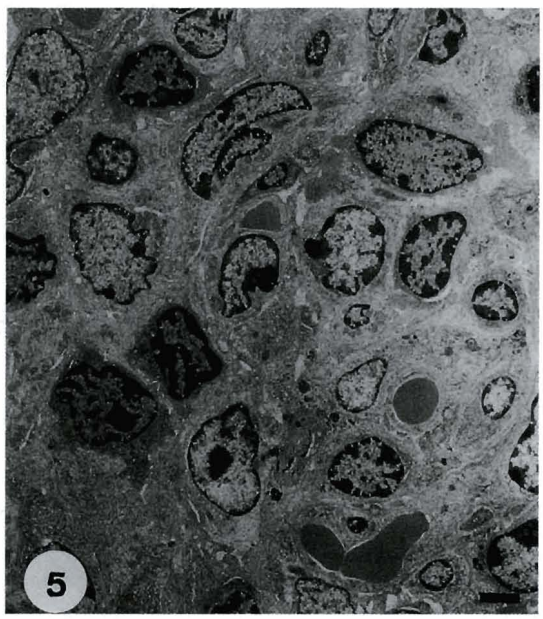


Fig. 5. Electron micrograph of the splenic white pulp of SCID mouse 24 hours after peroxidase anti-peroxidase (PAP) administration. There is no distinct PAP localization in the white pulp, which consists of frequent stromal cells and very rare lymphocytes. x 2,500; Bar: 2 μm.

2^k-negative. The present cell grafting study using Wistar rat bone marrow cells also clearly demonstrated the occurrence of FDC-M1-positive FDCs in the LFs of short-term reconstructed SCID mice. These data strongly indicate that FDCs are not derived from bone marrow but may have a stromal origin in SCID mice. However, the present observation period may be too short to reveal a potential contribution of donor bone marrow-derived FDCs. FDC-precursors may be rather slow to migrate and differentiate locally. An observation period of several months may be necessary.

In conclusion, the present study demonstrated that functional LFs and FDCs appear in short-term reconstructed SCID mice, and that FDCs may not be derived from bone marrow cells.

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