Signal Transmission through MHC Class II Molecules in a Human B Lymphoid Progenitor Cell Line: Different Signaling Pathways Depending on the Maturational Stages of B Cells

Keiko Naitoh1, Yasuhisa Ichigi1, Kensuke Miyake1, Atsushi Muraguchi2, and Masao Kimoto*,1

1Department of Immunology, Saga Medical School, Saga, Saga 849, Japan, and 2Department of Immunology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Toyama 930-01, Japan

Received June 13, 1994; in revised form, August 5, 1994. Accepted August 23, 1994

Abstract: The function of MHC class II HLA-DR molecules expressed on a human B lymphoid progenitor cell line FL8.2.4.4 (abbreviated as FL4.4) was examined. FL4.4 cells expressed HLA-DR molecules and stimulation of the DR molecules by anti-DR mAb or by superantigen TSST-1 induced strong augmentation of homocytic aggregation and protein tyrosine phosphorylation in FL4.4 cells. Induced homocytic aggregation in FL4.4 consists both of LFA-1/ICAM-1-dependent and -independent pathways as revealed by mAb blocking experiments. Metabolic inhibitors, NaN3 and cytochalasin B, blocked the induced homocytic aggregation of FL4.4. Early mature Daudi B cell lines also showed a similar type of homocytic aggregation by stimulation with anti-DR mAb. Daudi cells are more sensitive to protein kinase inhibitors herbimycin A and H7 than FL4.4 cells in their blocking of induced homocytic aggregation, while W7 showed stronger inhibitory effects on FL4.4 cells than on Daudi cells. Western blotting analysis revealed that the stimulation of DR molecules induced protein tyrosine phosphorylation of 100-kDa, 90-kDa, 60-kDa and 55-kDa proteins in FL4.4 cells, while, in Daudi cells 110-kDa, 100-kDa and 80-kDa proteins were phosphorylated. These results suggest that different signaling pathways through class II molecules are employed depending on the maturational stage of B-cell differentiation.

Key words: Human B progenitor cell, MHC class II, Protein tyrosine phosphorylation, Homocytic aggregation

Class II molecules encoded by the major histocompatibility complex (MHC) are transmembrane glycoproteins consisting of 34-kDa α chains non-covalently associated with 29-kDa β chains (18). In humans, at least three kinds of class II molecule isotypes exist, namely HLA-DR, -DQ and -DP. These class II molecules are shown to be expressed on B cells, macrophages and activated T cells (37). Recent crystallographic studies demonstrated that antigenic peptides are trapped within the groove created by α1 and β1 domain of each chain where highly polymorphic amino acid residues exist (2). These antigenic peptides in conjunction with the helix structure of α1 and β1 domains are recognized by antigen-specific T cells, which is one of the initial events in specific immune responses.

In addition to T-cell stimulation, recent studies suggested that the class II molecule functions as a signal transducer molecule. Thus, the recognition of class II/antigenic peptide complexes by antigen-specific T-cell receptors transduces activating signals to several species of cellular proteins in B lymphocytes and macrophages (40). Stimulation of class II molecules by anti-class II antibodies or by several kinds of superantigens were reported to induce homocytic adhesion (16, 17, 28, 32), increase of intracellular [Ca2+]i concentrations (15, 21, 26), cytokine-assisted cellular proliferation and differentiation (4, 27) and induction of B7 molecule expression (30) and IL-1β and TNFα transcription (38) in normal B lymphocytes as well as in B

Abbreviations: H7, 1-(5-isoquinolynyl sulfonyl)-2-methympiperazine; ICAM-1, intercellular adhesion molecule-1; LFA-1, lymphocyte function-associated antigen-1; TSST-1, toxic shock syndrome toxin-1; W7, N-(6-aminohexyl)-5-chloronaphthalene-1-sulfonamide hydrochloride.
lymphoblastoid cell lines. Recently, these phenomena are reported to be associated with elevation of cAMP, nuclear translocation of protein kinase C or activation of tyrosine kinases (1, 3, 6, 11, 16, 34, 36). These studies, however, are confined to mature B cells and pre-B cells. Little is known about the function of class II molecules expressed in very early lymphoid lineage cells.

Recently, we (29, 39) as well as others (13) have successfully established B lymphoid progenitor cell lines derived from EBV-transformed human fetal liver cells. We also succeeded to isolate clones derived from such lymphoid progenitor cell lines (14). Several clones derived from such lymphoid progenitor cell lines expressed HLA-DR, CD19, CD20 and CD2 on the cell surface but retained the germ line configurations in both Ig and TCR genes, suggesting that these clones belong to the earliest cell lineage of B cell differentiation (14, 29). In this paper, we analyzed the function of HLA-DR molecules expressed on one of such B lymphoid progenitor clone, FL8.2.4.4 (abbreviated as FL4.4). We observed that the stimulation of class II molecules on FL4.4 cells by anti-DR mAb or by superantigen TSST-1 induced augmentation of homocytic aggregation and protein tyrosine phosphorylation. Interestingly, different species of protein tyrosine are phosphorylated in FL4.4 and Daudi cells. Although the physiological functions of class II molecules on such B lymphoid progenitor cells remain to be elucidated, our studies suggest strongly that they function as signal transducer molecules and are speculated to be involved in the maturation of the B lineage cells. Also, our results suggest that the signals transmitted through class II molecules employ different signaling pathways depending on the maturational stage of B-cell differentiation.

Materials and Methods

**Chemicals and reagents.** Toxic shock syndrome toxin-1 (TSST-1), NaN3, 2-deoxyglucose, cytochalasin B, cyclohexamide, 1-(5-isoquinolynyl sulfonyl)-2-methylpiperazine (H7), N-(6-aminohexyl)-5-chloronaphthalene-1-sulfonamide hydrochloride (W7), EDTA, avidin and PMA were purchased from Sigma Chemicals (St. Louis, Mo., U.S.A.). Herbimycin A was obtained from Wako Pure Chemical Industries (Osaka, Japan).

**Antibodies.** Anti-HLA-DR mAb 3G7II (HU4) was made by Dr. M. Aizawa (Hokkaido University) (19) and kindly provided by Dr. Y. Nishimura (Kumamoto University). Anti-LFA-1 mAb (TS1/22) was obtained from ATCC. Anti-ICAM-1 mAb (84H10) was purchased from Immunotech (Mar- seille, France).

**Cell lines.** A cell line FL8.2 was established by EBV transformation of 8 weeks human fetal liver cells as described previously (14, 29). A clone FL8.2.4.4 (abbreviated as FL4.4) was established by the limiting dilution technique from FL8.2 cell line. The characterization of FL4.4 clone is summarized in Table 1. FL4.4 is HLA class I +, DR +, CD45 +, CD2 +, CD3 -, TCR α/β -, TCR γ/δ -, CD4 -, CD8 -, CD19 +, CD20 + and does not express cytoplasmic or surface μ-chain. The Ig/TCR genes are germ-line configurations. A human mature B lymphoid cell line Daudi was obtained from Japan Cell Resources (Tokyo). Cell lines used in this paper were maintained in the culture medium which consisted of RPMI 1640 (GIBCO, Grand Island, N.Y., U.S.A.) supplemented with 10% fetal calf serum (FCS, GIBCO), 5 × 10⁻⁵ M 2-mercaptoethanol, 100 U/ml penicillin, 100 μg/ml streptomycin. L-Glutamine (GIBCO) was added at a final concentration of 2 mM before use.

**Homocytic aggregation assay.** Cells were washed with HBSS and suspended in a culture medium.
Four to \(6 \times 10^4\) cells were cultured in 0.2 ml culture medium in a 96-well microtiter plate (Falcon No. 2075). Varying concentrations of mAbs or superantigens were added at the initiation of the culture. In the inhibition assay, cells were pre-incubated with various inhibitors for 30 min before stimulation with mAbs. Semi-quantitative scoring of adhesion was carried out as described (16) after culturing for 4 hr: 0), no adhesion or cell cluster formation was observed (>90% of the cells were unaggregated); 1), the majority of cells were unaggregated but small clusters of 10 to 20 cells were observed; 2), approximately 50% of the cells were medium-sized aggregated with the remainder as single cells; 3), nearly all the cells were medium-sized to large aggregates with only a few (<20%) unaggregated cells; 4), >90% of the cells were in large aggregates. For electron microscopic analysis, cells were washed and cultured in the presence of 1 \(\mu g/ml\) of anti-DR mAb for 4 hr, pelleted, fixed with 3% glutaraldehyde and examined by transmission electron microscopy.

*Flow cytometric analysis.* One \(\times 10^6\) cells were first incubated with 20 \(\mu l\) of appropriately diluted mAb for 30 min at 4 C. Cells were washed three times with cold phosphate-buffered saline (pH 7.2) containing 1% FCS and 0.1% NaN3 (staining buffer). Twenty microliters of appropriately diluted second antibody was added and incubated for 30 min at 4 C. Twenty microliters of 10 \(\mu g/ml\) propidium iodide (Sigma) was added for the last 5 min to exclude dead cells from the analysis. Cells were then washed three times with cold staining buffer and analyzed by FACScan (Becton-Dickinson Immunocytometry Systems, Mountain View, Calif., U.S.A.).

*Western blotting with anti-phosphotyrosine mAb.* This was performed as described (22) with slight modifications. One \(\times 10^6\) cells were stimulated with anti-DR mAb at 37 C in 1 ml culture medium. Cells were pelleted by centrifugation and lysed directly with 100 \(\mu l\) of boiling SDS sample buffer containing 20 \(\mu M\) sodium orthovanadate (Sigma). Samples were boiled for 5 min, separated by 8% SDS-PAGE and transferred to the nitrocellulose filter (Schleicher and Schuell, Dassel, Germany) in the transfer buffer (25 mM Tris, 192 mM glycine, 20% methanol). The filter was blocked with 5% BSA in Tris-buffered saline (pH 8.0) overnight at 4 C, and protein tyrosine phosphorylation was detected by Western blot with monoclonal anti-phosphotyrosine mAb PY20 (ICN Immuno-Biologicals, Costa Mesa, Calif., U.S.A.) in combination with \(^{125}\text{I-}\)protein A (Amersham, Arlington Heights, Ill., U.S. A.). Data was analyzed using BAS2000 Image Analyzer (Fuji Film Co., Tokyo).

**Results**

*Induction of Homocytic Aggregation in FL4.4 and Daudi Cell Lines by Stimulation with Anti-DR mAb or TSST-1*

FL4.4 and Daudi cells were cultured with monoclonal anti-DR mAb 3G7II for 4 hr. FL4.4 cells showed a moderate degree of spontaneous homocytic aggregation in the absence of stimulation. When stimulated with anti-DR mAb, strong homocytic aggregation was induced in both FL4.4 and Daudi cells (Fig. 1, A and B). FL4.4 cells aggregate in a large clump while Daudi cells make aggregates of chain-like morphology. Similar chain-like aggregation of Daudi cells was reported by other investigators (8) which may reflect unique characteristics of this cell line. The degree of aggregation of Daudi cells stimulated by anti-DR (1 \(\mu g/ml\)) or TSST-1 (1 \(\mu g/ml\)) was maximum for this cell line and scored as “3” according to the criteria described in “Materials and Methods.” Electron microscopic analysis revealed marked interdigitation in both aggregated FL4.4 and Daudi cells (Fig. 1C). No remarkable changes were observed in cytosolic organs or in nuclei. The induced homocytic aggregation was partially blocked by the addition of anti-LFA-1 or anti-ICAM-1 mAb or combination of both, indicating that both LFA-1/ICAM-1-dependent and -independent cell adhesion pathways are involved in such anti-DR mAb induced homocytic aggregation (Fig. 1, A and B). Stimulation with PMA, which is known to induce LFA-1/ICAM-1-dependent aggregation (16, 28), induced strong homocytic aggregation in FL4.4 cells. PMA induced no aggregation of the Daudi cells. The degree of aggregation induced by anti-DR mAb was dose-dependent (Fig. 2A). The addition of EDTA completely inhibited homocytic aggregation (Fig. 2B), suggesting that all the induced and spontaneous adhesion pathways are dependent on the presence of Ca\(^{2+}\) and/or Mg\(^{2+}\). We next tested several superantigens which are known to bind class II molecules for the induction of homocytic aggregation of FL4.4 and Daudi cells. TSST-1 dose-dependently induced homocytic aggregation in both of these cell lines as shown in Figs. 1 and 2. *Staphylococcus enterotoxin-A,* -B, and -E, however, did not induce homocytic aggregation in these cells (data not shown).
Since LFA-1/ICAM-1-dependent pathways were shown to be employed for the aggregation of FL4.4 and Daudi cells, we examined the amounts of these molecules on FL4.4 and Daudi cells before and after the stimulation with anti-DR mAb. As shown in Fig. 3, no increase of LFA-1 or ICAM-1 molecules was observed, suggesting that the induced homocytic aggregation was not due to the increased expression of LFA-1 or ICAM-1 molecules on these cells. Stimulation with PMA or TSST-1 also did not increase the expression of LFA-1 or ICAM-1 molecules.

**Inhibition of Homocytic Aggregation by Metabolic Inhibitors**

Next, the effects of various metabolic inhibitors on the induced homocytic aggregation were examined. As shown in Fig. 4, the combination of NaN₃ plus 2-deoxyglucose, which blocks ATP synthesis, inhibited dose-dependently anti-DR mAb induced homocytic aggregation of FL4.4 and Daudi cells. Cytochalasin B, inhibitors of the actin filament movement, also showed a strong inhibition of homocytic aggregation. In contrast, cycloheximide, which blocks protein synthesis did not completely block homocytic aggregation, suggesting that newly synthesis of cellular proteins is not absolutely required for the anti-DR mAb induced homocytic aggregation.

**Inhibition of Homocytic Aggregation by Protein Kinase Inhibitors**

To analyze the signals delivered through surface class II molecules, the effects of various protein
kinase inhibitors were examined. As shown in Fig. 5, herbimycin A, a tyrosine kinase inhibitor, strongly inhibited anti-DR mAb-induced homocytic aggregation of Daudi cells. The same concentration of herbimycin A showed a weak inhibitory effect on spontaneous or anti-DR mAb-induced homocytic aggregation of FL4.4 cells. DMSO, the diluent of herbimycin A did not inhibit homocytic aggregation at the concentration used (data not shown). H7, which inhibits the activity of protein kinase C, showed similar effects as herbimycin A. In contrast, inhibition by W7, which inhibits the calcium calmodulin-dependent protein kinase, is stronger in FL4.4 cells than in Daudi cells. These results suggest that activation of various protein kinases are involved in class II-mediated homocytic aggregation and also suggested that major signaling pathways employed in signaling through the class II molecules could be different in mature Daudi cells and progenitor FL4.4 cells.

**Protein Tyrosine Phosphorylation of FL4.4 and Daudi Cells by the Stimulation of Class II Molecules**

In order to examine whether the stimulation of DR molecules by anti-DR mAb or by TSST-1 induces phosphorylation of protein tyrosine, we performed Western blot analysis. Cells were stimulated with anti-DR mAb for various periods of time, pelleted and lysed by detergent and electrophoresed on 8% polyacrylamide gels. Cellular proteins were transferred to nitrocellulose filter and incubated with anti-phosphotyrosine mAb (PY20)
Fig. 3. Amounts of cell surface LFA-1 and ICAM-1 molecules after stimulation with anti-DR mAb, TSST-1 or PMA. FL4.4 and Daudi cells were stimulated with anti-DR mAb, TSST-1 or PMA as described in Fig. 1. Cells were then stained with biotinylated-anti-LFA-1 or biotinylated-anti-ICAM-1 mAb followed by FITC-avidin and analyzed by FACScan. Dead cells were gated out by staining with propidium iodide. Non-stimulated control cells stained with FITC-avidin only (-----). Non-stimulated cells stained with biotinylated anti-LFA-1 or biotinylated anti-ICAM-1 mAb plus FITC-avidin (------). Cells stimulated with anti-DR mAb, TSST-1, or PMA and stained with biotinylated anti-LFA-1 or biotinylated anti-ICAM-1 mAb plus FITC-avidin (---).

<table>
<thead>
<tr>
<th>Compound</th>
<th>FL4.4 LFA-1</th>
<th>FL4.4 ICAM-1</th>
<th>Daudi LFA-1</th>
<th>Daudi ICAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-deoxy glucose</td>
<td>2-deoxy glucose</td>
<td>2-deoxy glucose</td>
<td>2-deoxy glucose</td>
<td>2-deoxy glucose</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>1 µM</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>10 µM</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1% NaN₃</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 4. Inhibition of homocytic aggregation of FL4.4 and Daudi cells by various metabolic inhibitors. Varying concentration of 2-deoxyglucose plus 1% NaN₃, cytochalasin B or cycloheximide was added 30 min before stimulation with anti-DR mAb. Aggregation scores were counted as described in Fig. 2. Aggregation scores of cells without stimulation (-----) and cells stimulated with 1 µg/ml of anti-DR mAb (---).

<table>
<thead>
<tr>
<th>Compound</th>
<th>FL4.4 Aggregation</th>
<th>Daudi Aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-deoxy glucose</td>
<td>4 (-----)</td>
<td>4 (-----)</td>
</tr>
<tr>
<td>1% NaN₃</td>
<td>1 (-----)</td>
<td>1 (-----)</td>
</tr>
<tr>
<td>1 µM</td>
<td>3 (-----)</td>
<td>3 (-----)</td>
</tr>
<tr>
<td>10 µM</td>
<td>2 (-----)</td>
<td>2 (-----)</td>
</tr>
</tbody>
</table>

Fig. 5. Inhibition of homocytic aggregation of FL4.4 and Daudi cells by various protein kinase inhibitors. Varying concentrations of herbimycin A, H7 or W7 was added 30 min before stimulation with anti-DR mAb. Aggregation scores were counted as described in Fig. 2. Aggregation scores of cells without stimulation (-----) and cells stimulated with 1 µg/ml of anti-DR mAb (---).
followed by $^{125}$I-labeled protein A. As shown in Fig. 6, anti-DR mAb induced tyrosine phosphorylation in several species of cellular proteins in FL4.4 cells (100 kDa, 90 kDa, 60 kDa and 55 kDa) and in Daudi cells (110 kDa, 100 kDa and 80 kDa) as indicated by arrowheads. Interestingly, the 60-kDa and 55-kDa bands observed in FL4.4 cells showed decreased protein tyrosine phosphorylation 5 min after stimulation with anti-DR mAb which was reproducible in three independent experiments. These results suggest that different pathways are involved in protein tyrosine phosphorylation of mature and progenitor lymphoid cell lines. This may reflect the above observations that Daudi cells but not FL4.4 cells are relatively sensitive to herbimycin A and H7 in their blocking of anti-DR mAb-induced homocytic aggregation (Fig. 5). Densitometric scanning revealed that the relative intensity of phosphorylation by the stimulation with anti-DR mAb in FL4.4 cells (100-kDa and 90-kDa bands) is about three times less than that observed in Daudi cells (110-kDa, 100-kDa and 80-kDa bands) (data not shown).

Discussion

In this report, we described that stimulation of class II molecules on B lymphoid progenitor cells, FL4.4, by anti-DR mAb or superantigen TSST-1 induced augmentation of homocytic aggregation. The augmented homocytic aggregation was partially blocked by anti-LFA-1 mAb or anti-ICAM-1 mAb, suggesting that LFA-1/ICAM-1-dependent and -independent pathways are involved in such class II-mediated homocytic aggregation. The induced homocytic aggregation was blocked by the addition of metabolic inhibitors such as NaN$_3$ and cytochalasin B, indicating the requirements of new ATP synthesis and actin filament movements in homocytic aggregation. An early mature B lymphoblastoid cell line, Daudi, which did not show spontaneous homocytic aggregation, showed similar homocytic aggregation by stimulation with anti-DR mAb or TSST-1. The induced homocytic aggregation was partially inhibited by protein kinase inhibitors. In these experiments, Daudi cells are more susceptible to herbimycin A and H7 in their induced homocytic aggregation. Biochemical analysis showed that stimulation by anti-DR mAb induced different species of protein tyrosine phosphorylation in FL4.4 cells and Daudi cells. These results suggest that different signaling pathways through class II molecules are employed in B lymphoid progenitor cell lines and mature B lymphocyte cell lines. The employment of different signal transducing pathways depending on the maturational stages of lymphoid cells has already been suggested as signals transmitted through sIgM and MB-1 molecules (20, 22, 31). It also should be noted that quiescent B cells are led to increase cAMP concentrations by the class II mediated signals while IL-4 and antigen stimulated B cells are brought to a state where class II molecules transduce signals involving the tyrosine kinase-dependent activation of phospholipase C leading to $[Ca^{2+}]_{i}$ mobilization (5).

Our Western blotting analysis of protein tyrosine phosphorylation by the stimulation with anti-DR mAb revealed clear difference between FL4.4 cells and Daudi cells. Thus, by the stimulation with anti-DR mAb, FL4.4 cells showed protein tyrosine phosphorylation of 100-kDa, 90-kDa, 60-kDa and...
Homocytic aggregation occurs for B lymphoid lineages. It is somewhat difficult to speculate that such a homocytic aggregation observed in vitro? speculates that multiple adhesion molecules included, it would be reasonable to assume that integrins (8,17,32). The reason for the discrepancy noticed, however, that anti-DR mAb-induced homocytic aggregation is almost completely blocked by EDTA which suggests that the major adhesion pathways of FL4.4 and Daudi cells are mediated by the integrin-dependent adhesion system. Antibodies against β1 chain of integrin (SG/19) (25) did not block the anti-DR mAb-induced homocytic aggregation (data not shown). We were not able to examine all the integrin-dependent pathways in these homocytic aggregations due to the unavailability of appropriate mAbs. It is possible that unidentified molecules of the integrin family are involved in the homocytic aggregation. Other investigators reported, however, that anti-DR mAb-induced homocytic aggregation employs adhesion molecules other than intergrins (8,17,32). The reason for the discrepancy is not clear. If signal transduction through class II molecules is involved in the maturation of B lineage cells as described above, it would be reasonable to speculate that multiple adhesion molecules including integrins are involved in FL4.4 cells.

What is the physiological meaning of homocytic aggregation of B lymphoma cells observed in vitro? It is somewhat difficult to speculate that such a homocytic aggregation occurs for B lymphoid lineages in vivo where heterogeneous populations of lymphoid and non-lymphoid cells exist. Rather, functional activation of adhesion molecules on B lymphoid lineage cells would contribute to the T cell-B cell interaction for antibody production in the case of mature B cells. For B progenitor lineage cells, such activated adhesion molecules would contribute to the maturation by migrating from stromal cells of one type to another in the bone marrow, or from the bone marrow to the periphery. Homocytic aggregation of homogeneous B lymphoid cell lines would be a useful system for the analysis of functional activation of adhesion molecules involved in these physiological conditions.

It is a general observation that the amounts of class II molecules increase with the maturation of murine B lymphocytes. Immature murine B lymphocytes are reported to express small amounts of class II molecules on their surface (12,24,41). The FL4.4 cells described in this paper, however, express large amounts of class II DR molecules on their surface in spite of their characteristics of lymphoid progenitor lineage cells. Several human lymphoblastoid progenitor cells are reported to express fairly large amounts of class II molecules on their surface (9,10,33). The developmental regulation of the amounts of class II molecules may differ between human and murine lymphoid cells.

Several investigators suggest that class II molecules are involved in the maturation of B lineage cells. Thus, treating neonatal mice with anti-class II mAbs resulted in the profound diminution of B cells with relative preponderance of IgM+, IgD- cells (12). Recently, it was shown that anti-class II mAb completely blocked the maturation of B-cell development from B progenitor cells in stromal cell-dependent B-cell cultures and B-cell development was impaired in C57BL/6 mice harboring anti-sense DNA to I-A β-chain transgenes (24). In contrast, class II gene-knock out mice showed almost normal development of B lineage lymphoid cells (23) with a relative decrease of surface IgD+ B cells in one knock out strain (7). The role of class II molecules in B cell development is, therefore, still controversial. Also, the physiological ligand(s), if any, for class II molecules involved in the maturation of B cells remains to be elucidated. It could be that CD4-like molecules are expressed on the stromal cells in the microenvironments of B-cell maturation and stimulate class II molecules. Alternatively, products of environmental micro-organisms such as TSST-1, could bind to class II...
molecules and induce B cell maturation. It is clear, however, from the results described in this paper and in several reports by other investigators that class II molecules transduce signals in progenitor B lineage cells. If several subsets of human lymphoid cells express high amounts of class II molecules from the very early maturational stages, as represented in FL4.4 cells described in this report, it would be reasonable to speculate that they play an important role in the maturation of B cells. In fact, functional B-cell abnormality was observed in some patients with class II-deficient (type II) bare lymphocyte syndrome (35).

This work was supported in part by a grant from the Ministry of Education, Science and Culture, Japan and the Osaka Foundation for the Promotion of Clinical Immunology.

We thank Dr. Nishimura (Kumamoto Univ.) for giving us monoclonal antibodies. We also thank Dr. Yonemitsu for photograph of transmission electron microscopy. The authors thank Ms. Sachiko Baba for her skillful secretarial assistance.

References


