CD73 Is Involved in Lymphocyte Binding to the Endothelium: Characterization of Lymphocyte–Vascular Adhesion Protein 2 Identifies It as CD73

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Summary

We have recently described a monoclonal antibody (mAb) 4G4 recognizing a 70-kD molecule constitutively expressed on human endothelial cells and on subpopulations of lymphocytes. We showed that this molecule, which we named lymphocyte–vascular adhesion protein 2 (L-VAP-2), mediates lymphocyte adhesion to cultured endothelial cells. Protein sequencing of tryptic peptides from immunoaffinity-purified L-VAP-2 revealed sequence identity between L-VAP-2 and CD73 (ecto-5′-nucleotidase, E.C.3.1.3.5), and COS cells transfected with a CD73 cDNA were positively stained with the mAb 4G4, which recognizes L-VAP-2. mAb 4G4 was also able to partially inhibit the ecto-5′-nucleotidase activity of peripheral blood lymphocytes. Moreover, cross-precipitation studies performed with mAb 4G4 and a CD73 workshop mAb 1E9 showed that these two antibodies recognize the same molecule. Since the tissue distribution and biochemical characteristics of the two molecules are also similar, we conclude that L-VAP-2 and CD73 are the same glycoprotein. Adhesion experiments showed significantly increased binding of freshly isolated lymphocytes to COS cells transfected with a CD73 cDNA, as compared to mock-transfected COS cells, and binding of lymphocytes to CD73-expressing COS cells was inhibited by the presence of mAb 4G4 in the adhesion assay. CD73 is a glycosyl phosphatidylinositol–linked molecule previously shown to have a co-signalling role in T lymphocyte proliferation. Our data suggest that it also has a function in mediating lymphocyte adhesion to the endothelium.

The adhesive interactions between different cells of the immune system and recirculation of lymphocytes through different lymphoid organs are mediated by a variety of molecules belonging to several structural families. These adhesion molecules are expressed on the leukocyte and/or the endothelial cell surface, or they are part of the extracellular matrix. Of these adhesion molecules, the best characterized ones belong to the Ig superfAMILY or the selectin and integrin molecular families (reviewed in 1–3). Several novel adhesion molecules have recently been discovered, including the P-selectin ligand PSGL-1 (P-selectin glycoprotein ligand 1) or the E-selectin ligand ESL-1 (4, 5). We have previously described a novel adhesion molecule, lymphocyte–vascular adhesion protein 2 (L-VAP-2), which mediates lymphocyte adhesion to the endothelium (6). An mAb 4G4 recognizing L-VAP-2 was obtained from an immunization with synovial stroma and was used to study the tissue distribution and the function of the molecule. L-VAP-2 is constitutively expressed on cultured human endothelial cells, as well as on subpopulations of lymphocytes consisting predominantly of B cells and CD8+ T cells. The involvement of L-VAP-2 in lymphocyte binding to the endothelium was tested in vitro using cultured human umbilical vein endothelial cells (HUVEC) and freshly isolated PBL. mAb 4G4 consistently inhibited lymphocyte binding to HUVEC by ∼25%. In immunohistochemical analyses, subpopulations of venules stained positively in a number of human tissues. On tonsillar tissue sections, vessels, germinal center B cells, and the basal layer of the surface epithelium expressed L-VAP-2 (6). Immunoprecipitations from 125I-labeled endothelial cell lysates showed that L-VAP-2 is a 70-kD molecule under both reducing and nonreducing conditions (6). Based on the molecular size and the tissue distribution, L-VAP-2 was judged to be a novel molecule among those known to mediate lymphocyte adhesion to the endothelium.

In the present paper, we report the further characterization of the L-VAP-2 molecule, including the amino acid sequence of tryptic peptides obtained from immunoaffinity-purified protein. Our data on the cellular distribution, molecular size, and the protein sequence of the L-VAP-2 molecule expressed on endothelial cells were similar to those...
described for ecto-5'-nucleotidase (ecto-5'-NT) (7, 8). mAb 4G4 also reacted specifically with ecto-5'-NT COS cell transfectants. We therefore conclude that L-VAP-2 and ecto-5'-NT are the same molecule. Ecto-5'-NT has been designated as lymphocyte differentiation antigen CD73 and, although an involvement in several immunological events has been proposed for the molecule (7), little is still known about the exact role of the molecule in lymphocyte functions. In this report, we present evidence of a novel role for CD73 in mediating lymphocyte adhesion to endothelial cells.

Materials and Methods

Cells, Cell Lines and Antibodies. The HEC endothelial cell line (equivalent to EAHy-926) was a kind gift from Dr. H. Holthöfer (University of Helsinki, Helsinki, Finland). The COS-7 cell line was from the American Type Culture Collection (Rockville, MD). Human PBL were isolated using Ficoll-Hypaque (Histo-paque-1077; Pharmacia, Uppsala, Sweden). mAb 4G4 (mouse IgG1) recognizes L-VAP-2 and inhibits the binding of lymphocytes to cultured endothelial cells (6). Anti-CD73 mAb 1E9 was a kind gift of Dr. Linda Thompson (Oklahoma Medical Research Foundation, Oklahoma City, OK). Irrelevant isotype-matched mAb against chicken T cells (3G6) and an mAb against human γ heavy chain (HB43; American Type Culture Collection) were used as negative controls.

Immunoprecipitation and Protein Sequencing of L-VAP-2. For immunoprecipitation, 106 HEC cells were lysed in lysis buffer (1% Triton X-100, 0.15 M NaCl, 1.5 mM MgCl2, 0.01 M Tris, 1 mM PMSF, and 1% aprotinin) containing 1 mM PMSF. Insoluble material was removed by centrifugation, and the lysate was precleared by passing it sequentially through Sepharose CL-4B and columns of cyanogen bromide-activated Sepharose 4B beads and columns of cyanogen bromide–activated Sepharose 4B beads (Pharmacia) derivatized with normal mouse serum or irrelevant IgG, mAb. The lysate was then incubated with 5 ml of CnBr-activated Sepharose 4B beads derivatized with mAb 4G4. After washing the beads with washing buffer (100 mM NaCl, 0.15 M Na2HPO4, 0.2% sodium deoxycholate, 0.01% SDS, and 1% NP-40), the bound material was eluted with 50 mM triethylamine and lyophilized. The protein was resolved with SDS-PAGE (5—12.5%, nonreduced) and transferred to polyvinylidine difluoride (PVDF) membrane (ProBlott; Applied Biosystems, Inc., Foster City, CA) by electroblotting. The membrane was stained with Coomassie blue, and the 70-kD band was excised and subjected to trypsin digestion (sequencing grade; Boehringer Mannheim GmbH, Mannheim, Germany), as described by Fernandez et al. (9). The peptides were separated by HPLC (model 150 A; Applied Biosystems) equipped with a Vydac C18 column (2.1 × 150 mm). NH2-terminal sequence analysis of the peptides was performed on a protein sequencer (model 477A; Applied Biosystems) equipped with an on-line phenylthiohydantoin (PTH) amino acid analyzer (model 120A; Applied Biosystems).

Isolation of a CD73 cDNA and Construction of Expression Vectors. A full-length cDNA encoding CD73 was amplified by reverse transcription (RT) PCR from total RNA isolated from HEC cells and inserted into the expression vector pC3DNA3 (In-vitrogen Corp., San Diego, CA). Standard techniques were used for the RNA isolation, cDNA synthesis, PCR amplification using the CD73 specific primers GGGGATCCAGTTCACGCGC-CACAG and CCCCTGAGGCAAGGAGAATTTTGGT, subcloning procedures, and plasmid preparations (8, 10).

Transfection of COS Cells. COS-7 cells were transfected by electroporation with 20 μg of the CD73 expression plasmids or 20 μg of the pcDNA3 plasmid (mock transfection). 3 d after transfection, cells were detached with 5 mM EDTA, immunofluorescence stained as described earlier (6), and L-VAP-2 expression was detected with a FACSscan® (Becton Dickinson & Co., Mountain View, CA).

Radiolabeling and Immunoprecipitations. [35S]Methionine/[35S]cysteine labeling of HEC cells was performed as described previously (11). The lysates from the labeled cells were precleared three times with 50-μl aliquots of rabbit anti–mouse IgG derivatized protein A–Sepharose beads (Pharmacia). For immunoprecipitations, 15 μl of these beads were preloaded with 1 ml 100 μg/ml of purified 4G4 or 1E9 or a negative control mAb (3G6). Precleared lysates were mixed with the specifically coupled protein A–Sepharose beads and incubated for 4 h at 4°C for each sequential precipitation. After washing with washing buffer, antigens were eluted from the beads with 50 μl Laemmli’s sample buffer containing 5% mercaptoethanol, and were resolved in 5—12.5% SDS-PAGE.

Phosphatidylinositol-specific Phospholipase C (PI-PLC) Treatment. Freshly isolated PBL were resuspended in RPMI in the presence or absence of Bacillus thuringiensis PI-PLC (Oxford Glycosystems, Abingdon, UK) at 1 U/ml and incubated for 1 h under rotation at 37°C. Cells were washed twice and immunofluorescence staining for L-VAP-2 expression was performed as described previously (6).

Ecto-5'-NT Inhibition. Activity of PBL ecto-5'-NT was analyzed using a modification of a previously reported method (12, 13). [35S]Adenosine-5'-monophosphate ([35S]AMP; ICN Biomedicals, Inc., Irvine, CA) was converted into [35S]inosine by PBL ecto-5'-NT in presence of 30 μg/ml of purified mAb 4G4, anti-CD73 mAb 1E9, or negative control antibody 3G6. Substrate and product were separated by thin-layer chromatography, and the corresponding radioactivity was detected by autoradiography. Quantitation was performed by measuring the intensity of the dots by using the Microcomputer Imaging Device (MCID; Imaging Research Inc., Ontario, Canada).

Lymphocyte Binding to COS Cells. PBL were fluorescence labeled as described before (6), and were plated onto confluent monolayers of CD73- and mock-transfected COS cells in 96-well tissue culture plates. Cells were incubated for 45 min at 37°C, and fluorescence in each well was determined by a fluorometer (TiterTek Fluoroskan; Labsystems, Helsinki, Finland). Nonadherent lymphocytes were removed, and the percentage of bound cells was quantitated by comparing the mean fluorescence of eight identical wells with bound lymphocytes to the mean fluorescence of eight unwashed wells. In an other type of adhesion assay, CD73–transfected COS cells were plated on eight-well permanox chamber slides (Nunc Inc., Naperville, IL) that had been precoated overnight in PBS at 37°C. PBL were added onto the chamber slides, and incubation was continued at 37°C for 45 min. The wells were then gently washed twice with warm RPMI to remove unbound lymphocytes, after which immunoperoxidase staining of the remaining cells was gently performed as described earlier (6). 3% glutaraldehyde was added to the wells, and lymphocyte binding to CD73-positive cells (10—40% of all cells, depending on the experiment) vs CD73-negative cells was evaluated under light microscopy. To study the effect of mAb 4G4 on lymphocyte adherence to CD73-transfected COS cells, PBL and the transfected COS cells on permanox chamber slides were pre-
treated with mAb 4G4 a hybridoma supernatant or negative control antibody (against human \( \gamma \) heavy chain or a nonbinding mAb 3G6). The adhesion assay and immunoperoxidase staining were performed as described above, and the effect of mAb 4G4 on lymphocyte adherence to COS cells expressing CD73 was examined by light microscopy in a blind assay, where the number of lymphocytes binding to CD73-positive COS cells in presence of the 4G4 mAb was counted in six different microscopic fields. This binding was compared to binding in the presence of 3G6 mAb, anti-\( \gamma \) mAb, or medium only (= Neg. Co).

**Statistical Analyses.** The results are expressed as mean values ± SEM. Statistical significance was evaluated by the two-tailed unpaired Student’s \( t \) test in case of adhesion experiments and by the paired Student’s \( t \) test in case of enzyme inhibition experiments.

**Results and Discussion**

Since L-VAP-2 is abundantly expressed on cultured endothelial cells, a HEC cell lysate was used for immunoaffinity purification to further characterize the molecule. Protein sequencing of tryptic peptides obtained from the purified material revealed sequence identity between L-VAP-2 and the CD73 molecule. The peptide sequences from tryptic peptides designated tryptic 19, 24, and 32 yielded amino acid sequences VIYPA, LDVLXTK, and GNVISSXGNPI, which are identical to the sequence of CD73 between positions 537–541, 472–478, and 298–308, respectively (8).

To confirm that L-VAP-2 and CD73 are the same molecule, a full-length CD73 cDNA was isolated by R.T-PCR from HEC cells and used to transfect COS cells. The COS cells transfected with a CD73 cDNA were positive when stained with mAb 4G4, which recognizes L-VAP-2 (Fig. 1), or with an anti-CD73-mAb 1E9, whereas mock-transfected COS cells were negative (Fig. 1).

To further demonstrate that 4G4 mAb is recognizing CD73, sequential immunoprecipitations were performed with mAb 4G4 and the anti-CD73 mAb 1E9. Immunoprecipitation with protein A-Sepharose coupled with 1E9 mAb completely removed the 70-kD protein recognized by mAb 4G4 from \(^{35}S\)methionine/\(^{35}S\)cysteine–labeled HEC cell lysate (Fig. 2). Similarly, 4G4 completely removed the 70-kD protein detected by 1E9 mAb in the first round of immunoprecipitations (Fig. 2). In addition, the 1E9 mAb precipitated a smaller ~60-kD protein (faintly visible), which was not recognized by mAb 4G4 and may be a nonglycosylated precursor of CD73. All of the lymphocyte surface molecules recognized by mAb 4G4 were sensitive to PI-PLC treatment, as shown by immunofluo-

![Figure 1](image1.png)

**Figure 1.** Flow cytometric analysis of mock-transfected COS cells or COS cells transfected with a CD73 cDNA. COS cells were transfected with CD73 cDNA or plasmid only and stained with antibodies 4G4, 1E9 (a CD73 workshop mAb), and 3G6 (Neg. Co), as described in Materials and Methods.

![Figure 2](image2.png)

**Figure 2.** mAbs 4G4 and 1E9 cross-precipitate each other. After \(^{35}S\)methionine/\(^{35}S\)cysteine labeling, the HEC cells were lysed. The precleared lysate was then sequentially precipitated with the mAbs (indicated above the individual lanes; 3G6 is a negative control antibody) coupled to protein A-Sepharose beads via rabbit anti-mouse Ig. Molecular weight standards in kilodaltons are indicated on the right. IP, immunoprecipitation.
from our adhesion experiments are the first evidence that lymphocyte binding to cultured endothelial cells (6). Since characteristics in lymphocyte functions, has led to the proposal that CD73 could have a role in lymphocyte homing and activation through the CD3/TCR signalling pathway has been indicated (19, 20).

L-VAP-2 and CD73 are shown to be identical, the data previously characterized CD73 workshop mAbs or to a novel epitope. CD73 has been shown to have a role in mediating lymphocyte adhesion. To confirm this, lymphocyte binding to transfected COS cells was analyzed. In these experiments, it was seen that adherence was significantly increased to COS cells transfected with CD73 cDNA, as compared to mock-transfected COS cells ($P = 0.016$; Fig. 5 A). In four individual experiments performed with freshly isolated, fluorescence-labeled lymphocytes and either mock-transfected or CD73-transfected COS cells (transfection efficiency $\sim 10\%$), $32 \pm 5\%$ of lymphocytes bound to CD73-transfected COS cells, whereas only $25 \pm 4\%$ of lymphocytes bound to mock-transfected COS cells. This corresponds to a $28 \pm 5\%$ increase in lymphocyte binding to CD73-transfected COS cells, as compared to mock-transfected COS cells (Fig. 5 A). Since only $10\%$ of COS cells were expressing CD73 in these experiments, we then used another type of binding assay to demonstrate that the lymphocytes actually bind to the CD73$^+$ population of COS cells. In this assay, after removing unbound lymphocytes from chamber slides, the transfected COS cells and the rightly bound lymphocytes were stained with the mAb 4G4 to visualize the CD73$^+$ COS cells. It was seen that lymphocytes preferentially bound to the positively stained COS cells expressing CD73, whereas the CD73$^-$ COS cells had significantly fewer lymphocytes attached to them (Fig. 5 B). The nature of this lymphocyte binding to CD73$^+$ COS cells was quite strong, since the lymphocytes were not detached during the gentle washing procedures included in the peroxidase staining protocol after the binding assay. In some of the experiments, CD73-transfected COS cells and lymphocytes were pretreated with the mAb 4G4, and an inhibition of $41 \pm 7\%$ could be seen in lymphocyte binding to CD73$^+$ COS cells, as compared to the binding of cells pretreated with a negative control antibody or medium only (Fig. 5 C). Thus, we have shown here that CD73 is involved in mediating lymphocyte adhesion by demonstrating that lymphocytes bind more avidly to CD73$^+$ than to CD73$^-$ COS cells and by blocking lymphocyte adhesion to CD73$^+$ COS cells by an anti-CD73 antibody.

**Figure 4.** Inhibition of ecto-5'-NT activity obtained by different anti-CD73 mAbs. Conversion of $[^3]C$AMP to $[^3]C$adenosine and $[^3]C$inosine by PBL-ecto-5'NT in the presence of mAbs 4G4, 1E9, and 3G6 was quantitated as described in Materials and Methods. The results shown are the mean of four samples with mAb 4G4 and three samples with mAb IE9 from two individual experiments $\pm$ SEM.

**Figure 3.** CD73 expression on PBL is reduced after PI-PLC treatment of cells. FACS$^+$ profiles are shown from (A) PBL stained with irrelevant mAb 3G6, (B) PBL stained with the anti-CD73 mAb 4G4, and (C) PI-PLC-treated PBL stained with mAb 4G4. In B, the arrow points to the CD73-positive population of PBL (15\% of all cells).
The exact mechanisms responsible for CD73-mediated adhesion are not clear at the moment. Either direct receptor–ligand binding or CD73-mediated intracellular signaling controlling the function of other adhesion molecules may be responsible for the lymphocyte adhesion observed; antibody binding to CD73 was recently shown to induce tyrosine phosphorylation and dephosphorylation of lymphocyte intracellular proteins, the identities of which are unknown at the present time (21). Interestingly, extracellular adenosine, which in vivo is produced by ecto-5′-NT activity, has previously been shown to regulate neutrophil binding to the endothelium (22). The enzymatic activity of CD73 may therefore also be involved in controlling lymphocyte adhesion.

In conclusion, we have shown that L-VAP-2 is identical to CD73. We also directly demonstrate the involvement of CD73 in mediating lymphocyte adhesion by blocking lymphocyte binding to CD73-expressing COS cells with an antibody against CD73. The exact mechanisms responsible for this novel function are under investigation.

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