

Ly-49 Mediates EL4 Lymphoma Adhesion to Isolated Class I Major Histocompatibility Complex Molecules

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Summary

Ly-49 is a recently identified cell surface molecule expressed on a subpopulation of natural killer (NK) cells and certain T lymphomas. It has been suggested, based on gene transfection and antibody blocking studies, that Ly-49 is a negative regulator of NK lytic activity, possibly through an interaction with target cell class I molecules. However, it has not been demonstrated that class I molecules indeed serve as ligands for Ly-49. We have found that T lymphomas expressing Ly-49 bind isolated class I major histocompatibility complex (MHC) molecules but not class II molecules immobilized on plastic. Adhesion to class I molecules was not found with T lymphomas lacking Ly-49 expression. The Ly-49 expressing EL4 lymphoma bound Dα, Dk, and Kb, but not Kd, Kk, or Db, thus demonstrating a restricted pattern of class I adhesion. The observed cell adhesion was class I density dependent, and binding to Dα and Dk was extensively inhibited by the A1 monoclonal antibody directed against Ly-49. These results provide direct evidence for Ly-49 serving as a receptor for a subset of class I MHC molecules.

Ly-49 is a disulfide-linked cell surface homodimer that consists of two 44-kD subunits and is normally expressed on a subpopulation of NK cells in certain strains of mice (1, 2). The orientation of Ly-49 in the plasma membrane (COOH terminus to the cell exterior) is that of a typical type II membrane protein, and the extracellular domain demonstrates homology to the C-type lectins (1, 2). Ly-49 is the product of a gene belonging to a newly identified gene family that maps to a region on mouse chromosome 6 termed the “NK gene complex” (2). Products from other members of this gene family are also expressed on NK cells and, although structurally related, demonstrate considerable heterogeneity in primary sequence (3). A human multigene family has also been identified which shows homology to genes of the mouse NK gene complex (4).

Expression of certain class I MHC molecules on target cells can often, but not always, inhibit NK lysis (5). A class I MHC protective effect has been given strong support from studies showing that transfection of certain class I molecules can confer resistance to otherwise NK-susceptible targets (6, 7). Recently, it has been demonstrated that antibodies to Ly-49 significantly reduce protection from IL-2-activated NK lysin conferred by expression of transfected class I genes in normally NK-susceptible targets (7). These results suggested that Ly-49 may be a receptor for class I molecules and that, perhaps upon engagement, Ly-49 transmits a signal that negatively regulates NK lytic activity.

In addition to NK cells, Ly-49 is expressed on certain T lymphoma cell lines (1). Interactions of Ly-49-expressing T lymphomas with isolated MHC molecules were examined and evidence is provided to indicate that certain class I MHC products are indeed ligands for Ly-49.

Materials and Methods

Cell Lines. The T cell lymphomas EL4, EL4.IL-2 subline, YAC-1, and TIMI.4 were obtained from American Type Culture Collection (Rockville, MD). The EL4.IL-2 subline, unlike EL4, secretes IL-2 upon appropriate stimulation (8). All T lymphomas assayed for adhesion to MHC molecules, including those mentioned above and RDM-4, an AKR lymphoma, were grown in DMEM (GIBCO BRL, Burlington, ON, Canada) supplemented with 2% heat-inactivated FCS (HI-FCS) (Hyclone Laboratories, Logan, UT), 5% heat-inactivated defined calf serum (HI-DCS) (Hyclone Laboratories), 20 mM Hepes, 2 mM l-glutamine, and 100 µg/ml penicillin-streptomycin. The A20 B cell lymphoma was kindly provided by Dr. A. O’Rourke (Scripps Clinic, La Jolla, CA) and was grown in DMEM supplemented with 5% HI-DCS, 20 mM Hepes and 2 mM l-glutamine.

Class I and II Protein Purification and Immobilization. Class I MHC proteins were isolated from RDM-4 (H-2k) and EL4 (H-2b) grown as ascites in syngeneic AKR (H-2k) and C57BL/6 (H-2b) mice and from A20 (H-2d) cells grown in vitro. The H-2Kk, Dk, Kk, and Db proteins were purified by mAb-affinity chromatography as previously described (9). The H-2Dk and Kk molecules were purified from A20 cells by mAb-affinity chromatography methods previously described (9), with the following modification: H-2Dk and Kk were obtained by sequential passage of A20 cell lysates over a 34-5-8S (Dk-specific) column and an M1/42 (pan-H-2) column for Kk, rather than differential elution from a single M1/42 column.
The IA^d and IE^d molecules were purified from A20 lysates using MK-D6 and 14-4-4S columns as previously described (10). Purified MHC proteins were quantitated by bicinchoninic acid (BCA) protein determination (Pierce, Rockford, IL) and ELISA (9). Purity of the isolated MHC preparations was verified by SDS-PAGE and Coomassie brilliant blue or silver staining.

Purified MHC proteins were immobilized in microtiter wells (Falcon Microtest III; Becton Dickinson, Oxnard, CA) for cell adhesion assays as previously described (9). Briefly, MHC proteins in detergent were diluted in Dulbecco's PBS (D-PBS) and incubated in plastic microtiter wells for 1.5 h at room temperature. Unbound protein was removed by washing and remaining sites on the plastic blocked with a 2% FCS/D-PBS solution. A 1% solution of BSA (Fraction V; Sigma Chemical Co., St. Louis, MO) was used to bind control wells which were then blocked with 2% FCS/D-PBS.

Antibodies and Hybridoma Supernatants. mAbs used in these studies include A1, anti-Ly-49 (11); 53-6.72, anti-CD8 (12); GK1.5, anti-CD4, (13); H57-597, anti-TCR β chain (14); F23.1, anti-TCR Vδ8 (15), 34-5-8S, anti-D^d α1α2 domain epitope (16); 34-2-12S, anti-D^d α3 domain epitope (16) and 15-5-5S, anti-D^k (17) that were in the form of hybridoma supernatants or reconstituted ammonium sulfate precipitates from supernatants of hybridomas grown in Protein Free Hybridoma Medium-II (GIBCO BRL).

Assay of Cell Adhesion. The method used to determine cell adhesion in microtiter wells bearing MHC proteins has been described in detail (18). Briefly, cells were labeled by incubation for 1 h with 100 μCi Na251CrO4, washed, resuspended in DMEM containing 2% FCS, and added to wells at 10^5 cells/well in 0.1 ml. Plates were centrifuged for 1 min at 400 rpm and incubated for 1 h or the indicated time at 37 °C in a CO2 incubator. In experiments using mAbs directed against EL4 cell surface molecules, the purified antibodies or hybridoma supernatants were added to the cells in suspension 20 min before addition of the cells to the wells. In experiments employing mAbs directed against the plate-bound class I, hybridoma supernatants were incubated in wells bearing class I for 20 min before addition of EL4 cells. At the end of the cell incubation on MHC-coated plates, an aliquot of supernatant was harvested from all wells to determine spontaneous release, then unbound cells were removed, the well bottoms cut off, and radioactivity determined. Cell binding was calculated as percent cells bound = 100 x (cpm bound/total cpm – spontaneous cpm). Measurements were done in triplicate for each condition and error bars in the figures show standard deviation.

Results

T Lymphomas Expressing Ly-49 Bind Isolated Class I Molecules. We reasoned that if Ly-49 is a receptor for class I MHC molecules then T lymphomas that express Ly-49 might bind class I molecules. This was tested with three T lymphomas known to express Ly-49, EL4, EL-4.IL-2, and TIMI.4 (1) and two T lymphomas that do not express this molecule, YAC-1 and RDM-4 (data not shown). Radiolabeled cell adhesion was observed to H-2D^d but not IE^d or BSA coated wells by Ly-49-expressing cells, particularly EL4 and TIMI.4, whereas the Ly-49 negative cells did not bind any of the immobilized proteins to significant levels (Fig. 1). A significantly lower percentage of EL4.IL2 cells bound D^d in the adhesion assay than did EL4 (Fig. 1). We have determined that EL4.IL-2 expresses a substantially lower level of Ly-49 than EL4 using a FACScan® instrument (Becton Dickinson & Co., Moun-

![Figure 1](image1.png)

**Figure 1.** Ly-49-expressing T lymphomas bind immobilized D^d. Immunopurified H-2D^d or IE^d in detergent were diluted separately in D-PBS and immobilized at 0.07 μg/well in plastic microtiter wells as described in Materials and Methods. BSA (0.1 μg/well) was immobilized in control wells. The indicated T lymphoma cell lines were labeled for 1 h with Na251CrO4 and 10^5 cells were incubated in each well for 1 h at 37°C. Unbound cells were removed and cell binding was quantitated for individual plate wells by γ-counting as described in Materials and Methods. Spontaneous release for all cell lines was <5%. Results are represented as the mean percent of input cells bound and the SD from triplicate wells.

![Figure 2](image2.png)

**Figure 2.** Specificity and density dependence of EL4 binding to isolated class I molecules. Purified class I or II MHC molecules were immobilized at the densities indicated, as described in Materials and Methods. 51Cr-labeled EL4 cells (10^5) were added to each well and incubated for 1 h and cell binding was determined by γ-counting. Background binding of EL4 on wells bound with BSA and blocked with 2% FCS/D-PBS was determined to be 4%, and this value was subtracted to give the percent specific cell binding shown. Spontaneous 51Cr release for the EL4 cells was <5%.

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been preincubated with the following hybridoma supernatants as indicated: blocking of plate wells, 10 s 51Cr-labeled EL4 cells were added which had and 53-6.72, (CD8 specific), at a 1:8 dilution, or in medium alone (No Al(anti-Ly-49), H57-597 (anti-TCR-fl pan specific), GK1.5, (CD4 specific), Figure 3. Anti-Ly-49 blocks EL4 adhesion to class I MHC molecules. The percent specific EL4 cell binding was determined after 1 h of incubation. Results are shown as mean percent binding with SD from triplicate wells minus nonspecific cell adhesion to BSA-coated plates (<5%). Spontaneous release for the EL4 cells in A and B was <5%.

Antibodies Recognizing Distinct D^d Epitopes Block EL4 Adhesion to Affinity-purified D^d. Two antibodies specific for D^d, K5-8S, directed against an a1/a2 domain, and 34-2-12S, an a3 domain-specific antibody, significantly blocked EL4 adhesion to isolated D^d, as did anti-Ly-49 (A1), indicating that D^d is indeed the mAb affinity-purified molecule bound by Ly-49 on EL4 cells (Fig. 4). The 34-5-8S blocked more completely than did 34-2-12S, suggesting that the moity recognized by Ly-49 may reside in the polymorphic a1/a2 domains of D^d. Blocking of EL4 adhesion to D^d was not observed with an antibody directed against H-2D^d (Fig. 4).

Kinetics of EL4 Adhesion to D^d and D^k Class I Molecules. EL4 binding to D^d and D^k class I molecules was followed over time. EL4 adhesion was found to be fairly rapid, with half-maximal binding achieved in 10-20 min and maximal binding approached within an hour for D^d and D^k (Fig. 5). Binding was sustained for at least 4 h at nearly maximal binding levels, suggesting a very stable interaction. Maximal binding to D^k plateaus at a lower percentage of cells bound than D^d, consistent with the affinity of Ly-49 for D^d being greater than that for D^k.

Antibodies to Ly-49 Block EL4 Adhesion to D^d and D^k Class I MHC Molecules. The preceding results indicated that EL4 cells bind certain class I molecules. We attempted to block adhesion of EL4 cells with a variety of hybridoma supernatants or purified antibodies specific for Ly-49, the TCR, as well as CD4 and CD8, two molecules capable of binding MHC molecules which are not normally expressed on these cells. Substantial blocking of EL4 adhesion to D^d and D^k was observed in the presence of purified A1 (anti-Ly-49) antibody or A1 hybridoma supernatants, whereas purified antibodies or antibody-containing supernatants specific for a conserved TCR, p chain determinant, CD4 or CD8, had only modest effects on binding (Fig. 3, A and B). EL4 adhesion to isolated K^b is not blockable with any of these antibodies including A1 (data not shown), suggesting that K^b may not be bound by EL4 via TCR, CD4, CD8, or Ly-49. These results directly implicate Ly-49 as the membrane receptor mediating adhesion of EL4 to isolated D^d and D^k, but probably not to K^b.

Antibodies: A1 34-5 34-2 5S

Figure 3. Antibodies recognizing distinct D^d epitopes block EL4 adhesion to Affinity-purified D^d. One antibody or A1 hybridoma supernatants, whereas purified antibodies or antibody-containing supernatants specific for a conserved TCR, p chain determinant, CD4 or CD8, had only modest effects on binding (Fig. 3, A and B). EL4 adhesion to isolated K^b is not blockable with any of these antibodies including A1 (data not shown), suggesting that K^b may not be bound by EL4 via TCR, CD4, CD8, or Ly-49. These results directly implicate Ly-49 as the membrane receptor mediating adhesion of EL4 to isolated D^d and D^k, but probably not to K^b.

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Figure 4. Antibodies recognizing distinct D^d epitopes block EL4 adhesion to Affinity-purified D^d. One antibody or A1 hybridoma supernatants, whereas purified antibodies or antibody-containing supernatants specific for a conserved TCR, p chain determinant, CD4 or CD8, had only modest effects on binding (Fig. 3, A and B). EL4 adhesion to isolated K^b is not blockable with any of these antibodies including A1 (data not shown), suggesting that K^b may not be bound by EL4 via TCR, CD4, CD8, or Ly-49. These results directly implicate Ly-49 as the membrane receptor mediating adhesion of EL4 to isolated D^d and D^k, but probably not to K^b.

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Figure 4.
The NK cell repertoire differs between individuals expressing different class I MHC alleles and can be altered in mice by class I transgenes (21) or allogeneic bone marrow chimerism (22). In the case of Ly-49, expression is found on a subset of C57BL/6 (H-2b) NK cells but not on NK cells from D4, or H-2k-expressing animals (22). It has been proposed that a high-affinity interaction between D4 and Ly-49 may result in a potent negative signal leading to deletion of Ly-49+ NK cells or reduction of Ly-49 expression (22). Our results would suggest that the affinity of Ly-49 for D4 is indeed much higher than at least three other class I molecules (Kk, Kb, and Dd) to which EL4 binding could not be detected, and somewhat higher than a fourth (Dk), based on differences in class I density requirements for EL4 adhesion. The intermediate affinity of Ly-49 for Dk is still sufficient to protect target cells in NK assays in vitro and mediate negative selection or downregulation of Ly-49 expression observed in vivo.

It is possible that the reason a number of H-2b-expressing targets are lysed effectively by Ly-49+ NK cells is that Ly-49 has an affinity for Kb and Db products on these particular targets that is too low to negatively regulate NK cells. Perhaps the affinity of Ly-49 for Kb or Db is influenced positively or negatively by differences in the repertoire of endogenous peptides displayed by Kb or Db on a given target cell type. We found that Ly-49+ EL4 cells did not bind isolated Db isolated from EL4, however EL4 cells did bind isolated Kb molecules. Binding of EL4 to Kb is not inhibited by the Ly-49-specific A1 antibody (data not shown), suggesting that another, yet to be defined receptor, may mediate EL4 adhesion to the “self” Kb molecule. The inability of TCR-specific antibodies to block EL4 adhesion to Kk (data not shown) suggests that a high affinity “anti-self” TCR, is not likely to be responsible for the observed adhesion. Because of the potential complication of other uncharacterized receptor(s) on EL4 and TIMI.4 for Kk, interaction of Ly-49 with Kk may not be readily assessed using these T lymphomas.

Ly-49 and other molecules encoded within the NK complex show homology to a superfamily of type II transmembrane proteins including C-type (Ca2+ dependent), carbohydrate binding receptors (23). Although specific carbohydrates are the structures recognized by bona fide C-type lectins within this superfamily, the structural aspects enabling certain class I molecules to serve as ligands for Ly-49 have not been determined. We found that an antibody directed against the NH2-terminal α1/α2 domains of D4 (34-5-8S) was more effective than a membrane-proximal α2 domain (34-2-12S)-specific antibody at blocking EL4 adhesion, suggesting that some portion of the polymorphic α1/α2 domains of D4 may be particularly important for Ly-49 recognition. The adhesion assay system described in this report, using Ly-49-expressing lymphomas and isolated class I MHC molecules, may provide a valuable means by which class I structural requirements for Ly-49 recognition can be characterized.

Discussion

Our results demonstrate that the Ly-49 bearing EL4 T lymphomas binds isolated H-2Dd and Dd molecules in a density-dependent manner and that the adhesion is inhibitable by an antibody to Ly-49. The class I binding specificity seen with EL4 includes that predicted for Ly-49 on NK cells in a previous study (7). In that report, Dd and an H-2k product were suspected of being ligands because they conferred protection from Ly-49+ NK cell-mediated lysis, and the protection was diminished by antibodies to Ly-49 (7). We predict from our results that Dk is the H-2k haplotype product recognized by Ly-49-dependent cell adhesion to class I molecules described in this study defines a new type of receptor for class I molecules encoded in the murine NK complex.

It is well established that expression of certain class I molecules on target cells can confer resistance to NK lysis (5). Two alternative models have been proposed to explain the protective effect mediated by class I molecules: (a) class I molecules expressed on target cells bind target structure(s) essential for NK recognition, rendering them recognizable to NK (20); and (b) NK cells express receptors that directly interact with target cell class I molecules and upon engagement deliver negative signals to the NK cell, thus preventing lethal hit delivery (5). The Ly-49-dependent class I binding observed in this study provides evidence that strongly favors the second model. The nature of any regulatory signals that may be delivered by Ly-49 engagement with class I however, remains to be established.

The NK cell repertoire differs between individuals expressing different class I MHC alleles and can be altered in mice by class I transgenes (21) or allogeneic bone marrow chimerism (22). In the case of Ly-49, expression is found on a subset of C57BL/6 (H-2b) NK cells but not on NK cells from D4, or H-2k-expressing animals (22). It has been proposed that a high-affinity interaction between D4 and Ly-49 may result in a potent negative signal leading to deletion of Ly-49+ NK cells or reduction of Ly-49 expression (22). Our results would suggest that the affinity of Ly-49 for D4 is indeed much higher than at least three other class I molecules (Kk, Kb, and Dd) to which EL4 binding could not be detected, and somewhat higher than a fourth (Dk), based on differences in class I density requirements for EL4 adhesion. The intermediate affinity of Ly-49 for Dk is still sufficient to protect target cells in NK assays in vitro and mediate negative selection or downregulation of Ly-49 expression observed in vivo.

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