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ROSETTING OF ACTIVATED HUMAN T LYMPHOCYTES WITH AUTOLOGOUS ERYTHROCYTES
Definition of the Receptor and Ligand Molecules as CD2 and Lymphocyte Function–associated Antigen 3 (LFA-3)

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CD2 (known also as T11 [1], LFA-2 [2, 3], and the E rosette receptor [4]) is a T lymphocyte surface glycoprotein of 50–58 kD that appears early in thymocyte ontogeny and is present on all mature T cells (5). mAbs to CD2 inhibit Th cell antigen–stimulated proliferation and cytolytic T lymphocyte–mediated killing (2–4, 6). CD2 mAbs inhibit an early step in T lymphocyte–mediated killing, adhesion of the T lymphocyte to the target cell (7). The findings suggest that CD2-mediated adhesion facilitates interaction of T lymphocytes with other cells.

Curiously, CD2 mAbs also inhibit rosetting of T lymphocytes with E (4, 8). When human T lymphocytes are centrifuged with E of certain species and held at 4°C, they are found to adhere to multiple E in delicate rosettes (9, 10). Rosetting has long been used to purify T lymphocytes from peripheral blood, and clinically to enumerate T lymphocyte subpopulations (11). Rosetting does not involve the T cell antigen receptor. Sheep E rosette with essentially all human T lymphocytes in peripheral blood and with thymocytes and activated T lymphocytes (9). A small percentage of human peripheral blood T lymphocytes will form autologous rosettes with human E (12–14). Rosetting with autologous and allogeneic E is equivalent. The subpopulation that forms autologous rosettes mediates the autologous MLR (12, 15) and may thus be activated. Activated human T lymphocytes, i.e., thymocytes, T lymphoblasts, and T cell tumor lines, vigorously rosette with human E (16). Rosetting of human T lymphocytes with E from sheep, human, pig, and rabbit is inhibited by CD2 mAbs (8, 13, 17, 18), and thus it has been inferred that CD2 is an E rosette receptor. We recently purified CD2 to homogeneity and found that it inhibited sheep E rosetting and was absorbed by sheep E (19). This suggested to us that CD2 might bind to a similar ligand on human E.

We have previously defined (3, 20) an antigen-independent pathway of T lymphocyte adhesion to target cells that involves CD2 on the T lymphocyte and...
lymphocyte function–associated antigen 3 (LFA-3) on the target cell. LFA-3 is a glycoprotein of 55–70 kD that is broadly distributed on nonhematopoietic as well as hematopoietic cells (2, 3). mAbs to LFA-3 and CD2 inhibit a similar spectrum of antigen-specific T cytolytic and Th cell responses (3). Furthermore, thymocyte rosetting with thymic epithelial cells is dependent on CD2 on the thymocyte, and LFA-3 on the thymic epithelial cell (21). These findings led us to question whether autologous E rosetting was mediated by a CD2/LFA-3 interaction similar to that which is so important in physiologic T cell responses.

We have confirmed this hypothesis, and have used autologous E rosetting as a model system to examine molecular interactions between CD2 and LFA-3. We demonstrate that purified CD2 binds to LFA-3 on E. Furthermore, purified CD2 can mediate cell-cell adhesion (aggregation) of E by binding to LFA-3.

Materials and Methods

Cells. Fresh PBL or thymocytes were separated on lymphocyte separation medium (Ficoll and diatrizoate salts, density 1.077–1.080 g/ml at 20°C) (Bionetics, Kensington, MD). T lymphoblasts were obtained by stimulating PBL with 1 μg/ml PHA (Sigma Chemical Co., St. Louis, MO) in RPMI 1640/10% FBS for 5 d, and they were washed in RPMI 1640/10% FBS three times before use. Identical rosetting results were obtained with PHA-PBL that had been washed free of PHA and cultured 1 d before use. The Jurkat T lymphoma cell line was maintained in RPMI 1640 with 10% FBS. Where indicated, lymphocytes (5 × 10⁶/ml) in RPMI 1640/5% FBS were pretreated with 0.1% bromelain or 0.2 U/ml neuraminidase (Calbiochem-Behring Corp., La Jolla, CA) for 1 h at 37°C. Cells were washed three times in RPMI 1640/10% FBS before addition to the rosetting assay.

Monoclonal Antibodies. mAbs were TS2/18 (CD2), TS2/9 (LFA-3), TS1/22 (LFA-1) (2), control P3X63 (myeloma IgG1), E3 (human glycophorin) (22), D44 (complement receptor type 1 [CR1]) (23), and IA10 (decay-accelerating factor [DAF]) (24). A goat anti–human glycophorin serum (Dr. Cathryn John, Children’s Hospital, Boston, MA) was used at a dilution of 1:100.

Membrane Proteins. CD2 was purified to homogeneity from Jurkat or SKW3 T lymphoma lines by mAb affinity chromatography as previously described (19). CD2 was eluted from a TS2/18 CD2 mAb Sepharose column with 0.1 M Glycine HCl buffer, pH 2.75, containing 0.2 M NaCl and 0.2% Triton X-100. The eluate was immediately neutralized to pH 7.4 with 0.1 volume of 1 M Tris/HCl, pH 9.0, and used for further studies after appropriate dilution. Protein was determined on ethanol-precipitated CD2 according to Lowry (24a). LFA-1 was purified from the same SKW3 cell lysate using a TS1/22 (2) mAb Sepharose column linked in series to the CD2 mAb Sepharose column under identical chromatography and elution conditions.

Immunofluorescent Flow Cytometry (26). Cells were stained with undiluted culture supernatants containing mAbs, purified mAbs, or a subclass-matched irrelevant antibody (Ab). The second-step fluoresceinated sandwich reagent was goat F(ab')₂ anti–mouse IgG (H+L) (Cappel Laboratories, Cochranville, PA). When flow microfluorometry was used to analyze inhibition of anti-LFA-3 mAb binding by CD2, cells were preincubated with CD2, LFA-1, or control buffers for 1 h at 4°C in 20 μl of HBSS with 15% BSA. All samples receiving membrane proteins, including the zero point of titrations, were adjusted to the same detergent and buffer concentrations. mAbs were added in an additional 20 μl and incubated another 30 min. mAb concentrations were the lowest, that gave optimal

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1 Abbreviations used in this paper: Ab, antibody; CR1, complement receptor type 1; DAF, decay-accelerating factor; LFA, lymphocyte function–associated antigen; Tl1TS, Tl1 target structure.
Results

Flow cytometry confirmed the predicted expression of LFA-3 on human E (Fig. 1A) and revealed no crossreactivity of the LFA-3 mAb on sheep E (Fig. 1B). Calculation of fluorescence intensity (adjusted for differences in gain between samples) showed anti-LFA-3 binding on human E at a level of one-fourtieth the level of binding on a lymphoblastoid cell line from a normal donor (Fig. 1C).

Peripheral blood human T lymphocytes rosetted with sheep E but not with human E as previously reported (9, 10) (Table I). The human Jurkat T lymphoma cell line (which expresses 1–2 × 10^5 molecules of CD2/cell [19]) was much more efficient than PBL at rosetting with human E (Table I). CD2 mAb inhibited autologous rosetting (Table I, Exp. 2), as previously described (13, 18). Control mAbs to the T lymphocyte surface proteins T4, T8, T3, and LFA-1 did not inhibit human E rosetting (data not shown). Strikingly, LFA-3 mAb completely
inhibited rosetting of human T cells with human E (Table 1, Exp. 2). Control mab to glycoporphin and CR1 on human E had no effect. mAb to CD2 completely inhibited Jurkat T cell rosetting with human and sheep E, while the mAb to LFA-3 inhibited rosetting with human but not sheep E. The lack of effect of anti-human LFA-3 mAb on rosetting with sheep E was expected from its lack of reactivity with sheep E (Fig. 1).

The cell type on which CD2 and LFA-3 were functionally important in E rosetting was tested by pretreating only one cell type with the mAb (Table 1, Exp. 3). CD2 mAb was inhibitory only when T cells were pretreated, and LFA-3 mAb was inhibitory only when human E were pretreated.

These findings with a T cell tumor line were confirmed and extended with human thymocytes and T lymphoblasts (Table II). In contrast to peripheral T lymphocytes, thymocytes and PHA blasts rosetted efficiently with human E. Rosetting of these cells with human E was inhibited at the level of the T cell with CD2 mAb and at the level of the human E with LFA-3 mAb (Table II, Exps. 1 and 2).

Removal of cell surface sialic acid with neuraminidase, and partial removal of cell surface glycoproteins with proteases have previously been shown (18, 27) to enhance a variety of cell-cell interactions, including E rosetting, possibly by reducing charge-charge repulsion due to negative surface changes. Bromelain and neuraminidase treatment of PBL unmasked rosetting activity (Table II, Exp.
MOLECULAR BASIS OF AUTOLOGOUS ROSETTING

Table II
Effect of mAb on Rosetting of Human T Cells with Human E

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Percent Rosettes with Human E</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Exp. 1</td>
</tr>
<tr>
<td>T cell</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
</tr>
<tr>
<td>Anti-CD2</td>
<td>—</td>
</tr>
<tr>
<td>Anti-LFA-3</td>
<td>—</td>
</tr>
<tr>
<td>Anti-Glyco-</td>
<td>—</td>
</tr>
<tr>
<td>phorin</td>
<td>—</td>
</tr>
<tr>
<td>Anti-CR1</td>
<td>Control</td>
</tr>
<tr>
<td>—</td>
<td>Anti-CD2</td>
</tr>
<tr>
<td>—</td>
<td>Anti-LFA-3</td>
</tr>
<tr>
<td>—</td>
<td>Anti-Glyco-</td>
</tr>
<tr>
<td>—</td>
<td>phorin</td>
</tr>
</tbody>
</table>

Cells were pretreated with mAb as described in Table I.

3), and bromelain treatment of PHA-stimulated PBL increased the efficiency of rosetting with human E (Table II, Exps. 2 and 3). Pretreatment experiments again showed that CD2 mAb inhibited at the level of the T lymphocyte and LFA-3 mAb inhibited at the level of the human E. Bromelain or neuraminidase treatment of human E rendered them agglutinatable by LFA-3 mAb (data not shown); in no other case were cells agglutinated by LFA-3 mAb or CD2 mAb.

To determine if CD2 was functioning as a receptor for human E, we tested whether the purified receptor could competitively inhibit the T lymphocyte–E interaction. CD2 was solubilized with Triton X-100 from human T lymphoblast cell lines and purified by mAb affinity chromatography as described in Materials and Methods. BSA was added to CD2 preparations to bind detergent (28) and prevent damage to cells. Purified CD2 inhibited Jurkat T cell rosetting with human E (Table III), and inhibited Jurkat T cell rosetting with sheep E as previously described (19).

Inhibition of autologous rosetting with purified CD2 suggested solubilized CD2 could bind to E. Purified, 125I-labeled CD2 bound to human and sheep E (3–10% of input counts in different experiments). We tested whether pretreatment of human E with LFA-3 mAb would inhibit CD2 binding. 125I-labeled CD2 binding to human E was inhibited 99% by anti-LFA-3 (Table IV). 125I-CD2 binding to sheep E was not inhibited by LFA-3 mAb, as expected from the lack of reactivity of LFA-3 mAb with sheep E. Binding to either sheep or human E was unaffected by control mAb to LFA-1, glycoporphin, and CR1. Inclusion of CD2 mAb inhibited binding of 125I-CD2 to both cell types, showing that labeled CD2 binding was specific.

Reciprocal experiments were carried out to determine whether CD2 could competitively inhibit binding of LFA-3 mAb. E were preincubated with unlabeled
TABLE III

Inhibition by Purified CD2 of Human E and Sheep E Rosettes

<table>
<thead>
<tr>
<th>Exp.</th>
<th>CD2</th>
<th>Jurkat cells rosetting with human E</th>
<th>Jurkat cells rosetting with sheep E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/ml</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>ND</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

Purified CD2 antigen in 50 µl or a buffer control was mixed with 100 µl of 30% BSA. Jurkat cells in 70 µl were added to give a final total volume of 200 µl with the indicated final concentration of CD2 and were incubated for 30 min at 4°C before the E rosette assay. Exp. 1: SKW3 CD2 in 0.2% Triton X-100, 0.01 M Tris, pH 7.2, 0.15 M NaCl. Exp. 2: Jurkat CD2 in 0.1% Triton X-100, 0.01 M Tris, pH 7.2, 0.15 M NaCl. Controls had identical detergent and buffer concentrations.

TABLE IV

Inhibition of 125I-CD2 Binding by Anti-LFA-3 Antibody

<table>
<thead>
<tr>
<th>Antibody Specificity</th>
<th>Human E 125I-CD2 Bound (cpm ± SD)</th>
<th>Sheep E 125I-CD2 Bound (cpm ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor 1</td>
<td>Donor 2</td>
</tr>
<tr>
<td>X63</td>
<td>3,697 ± 55</td>
<td>5,329 ± 79</td>
</tr>
<tr>
<td>Anti-LFA-1</td>
<td>3,898 ± 40</td>
<td>5,547 ± 56</td>
</tr>
<tr>
<td>Anti-CR1</td>
<td>3,205 ± 79</td>
<td>5,135 ± 97</td>
</tr>
<tr>
<td>Anti-glycophorin</td>
<td>3,687 ± 20</td>
<td>5,524 ± 131</td>
</tr>
<tr>
<td>Anti-LFA-3</td>
<td>42 ± 24</td>
<td>57 ± 26</td>
</tr>
<tr>
<td>Anti-CD2</td>
<td>53 ± 14</td>
<td>34 ± 6</td>
</tr>
</tbody>
</table>

5 × 10⁶ human or sheep E were incubated with 50 µl of mAb (either hybridoma culture supernatant anti-CR1, anti-glycophorin, anti-CD2 and anti-LFA-3, or 1:100 diluted ascites X63 and anti-LFA-1) for 45 min at 4°C. Then 50 µl of 125I-CD2 (diluted to 4,000 cpm/µl with 10% FBS/RPMI 1640/2 mM Hepes, pH 7.4/3% BSA) was added and the incubation was continued for another 2 h at 4°C. After incubation, the cells were washed three times with 10% FBS/RPMI 1640/2 mM Hepes, pH 7.4 and were counted in a gamma counter.

CD2 or control purified protein (LFA-1), then treated with the TS2/9 mAb to LFA-3, washed, and stained with FITC-conjugated second antibody for analysis by flow cytometry. Purified CD2 inhibited in a dose-dependent fashion the binding of anti-LFA-3 to human E (Fig. 2). At 420 nM, CD2 reduced anti-LFA-3 binding to human E by 79% (Fig. 2A). Half-maximal inhibition was attained at ~30 nM CD2 (Fig. 2C). The binding of a control antibody (anti-DAF) was unaffected by CD2 (Fig. 2, B and C). As another control, preincubation with purified LFA-1 (1,000 nM) had no affect on anti-LFA-3 binding to human E (Fig. 2C). These experiments strongly suggest that CD2 binds directly to LFA-3 on human E.

Functional studies showed that purified CD2-mediated cell-cell adhesion (agglutination) of both human and sheep E (Fig. 3, B and F). Similar results were
obtained with CD2 that was freed from detergent by sedimentation through a sucrose gradient. Titration experiments showed that higher concentrations were required to mediate adhesion (420 nM, data not shown) than to inhibit LFA-3 mAb binding. Although we do not know the physical form of CD2 that mediates cell-cell adhesion in this assay, we believe that CD2 either integrates into the E membrane via a hydrophobic region or that it is present in a multimeric form, perhaps as protein micelles. Heat-denatured CD2 did not agglutinate E (Fig. 3D), showing that adhesive activity is dependent on CD2 protein conformation. Heat denaturation of CD2 also abrogates its ability to inhibit T cell–sheep E rosetting (19). Anti-LFA-3 mAb completely inhibited CD2-mediated human E
Figure 3. CD2 induced aggregation of E. 10⁷ E were mixed with 20 µg/ml CD2 with or without 5 µg/ml mAb in the presence of 15% BSA. The mixture was centrifuged for 2 min at 200 g and incubated on ice for 2 h. The cells were gently resuspended by rotating the tube and photographed with a Nikon inverted microscope at an original magnification of ×100 (×77 shown here), except for anti-glycophorin induced aggregation of human E which was photographed at ×40 (×31 shown here). (A) human E; (B) human E + CD2; (C) human E + CD2 + LFA-3 mAb; (D) human E + CD2 denatured at 100°C for 15 min; (E) sheep E; (F) sheep E + CD2; (G) sheep E + CD2 + LFA-3 mAb; (H) human E + anti-human glycophorin serum + LFA-3 mAb.
aggregation (Fig. 3 C), strongly suggesting that aggregation of human E by CD2 is mediated by direct binding of CD2 to LFA-3. As expected, anti-LFA-3 had no effect on aggregation of sheep E by CD2 (Fig. 3 G). As a specificity control, agglutination induced by a polyclonal serum to human glycophorin was unaffected by anti-LFA-3 (Fig. 3 H).

Discussion

We have found that autologous rosetting of human T cells with E is due to binding of CD2 on the T lymphocyte to LFA-3 on the erythrocyte, and have used this system to explore the interactions between these molecules. Antibodies to CD2 and LFA-3 inhibited rosetting by binding to the T lymphocyte and the E, respectively. These mAbs inhibited rosetting by thymocytes, mitogen-activated lymphocytes, and a T lymphoma tumor cell line. Peripheral blood T lymphocytes do not rosette, but rosetting activity that was unmasked by neuraminidase or bromelain treatment was CD2 and LFA-3 dependent. Detergent-solubilized, purified CD2 bound to LFA-3 on E, as demonstrated by inhibition by LFA-3 mAb of CD2 binding and reciprocal inhibition by CD2 of LFA-3 mAb binding. Higher concentrations of purified CD2 (400 nM) aggregated E and this aggregation was inhibited by LFA-3 mAb. These results show that CD2 binds to LFA-3 on E, and that this interaction is sufficient to mediate cell-cell adhesion.

CD2 and LFA-3 previously have been shown to participate in a pathway of antigen-independent adhesion of T cells to B lymphoblastoid target cells (20), and to be important in both T cytolytic and Th cell function (1–7). In studies analogous to those reported here (29), purified CD2 has been shown to bind to LFA-3 on a B lymphoblastoid cell line. Antigen-specific cytolytic T lymphocyte-mediated killing of this cell line has been shown to be inhibited by CD2 mAb and LFA-3 mAb (2). Thus, functionally important T cell–target cell interactions and autologous rosetting involve similar interactions at the molecular level between CD2 and LFA-3. In further similarity to the human E rosetting system studied here, CD2- and LFA-3-dependent (but not LFA-1-dependent) antigen-independent conjugate formation can occur at 4°C (20). The concentration at which CD2 inhibited LFA-3 mAb binding suggests that the affinity of CD2 for LFA-3 on E is ~3 × 10^7/M; this is similar to its affinity for LFA-3 on B lymphoblastoid cells of ~1.9 × 10^7/M (29). Autologous rosetting is thus not an aberrant crossreaction; rather, it is an interesting model system for studying a physiologically relevant molecular interaction.

A particularly interesting feature of autologous rosetting is its dependence on T cell activation. Thymocytes and T cell blasts, but not peripheral blood lymphocytes, form autologous rosettes, correlating with expression of activation epitopes on the CD2 molecule (1, 30). Whether CD2 from activated cells has a higher affinity for LFA-3 than CD2 from resting peripheral T lymphocytes is an interesting question for further work. Activation epitopes can be induced on CD2 on resting T lymphocytes at 4°C in 2 min (1, 30, 31), raising the possibility that detergent solubilization could also change the conformation of CD2 and alter its affinity for LFA-3. We found that latent CD2- and LFA-3-dependent rosetting by peripheral T lymphocytes could be unmasked by protease or neuraminidase treatment. A reduction of net negative surface charge, lessening
charge repulsion between the T lymphocyte and E would be sufficient to explain these effects, but it is possible that modification of CD2 is also important. Neuraminidase treatment of T cells has been shown to unmask CD2 activation epitopes (30).

Although we found no rosetting of peripheral blood T lymphocytes with human E, under less stringent conditions a small percentage of peripheral blood T lymphocytes are found to form autologous rosettes (12–14). Removal of these cells abrogates the autologous mixed lymphocyte reaction (12–14). The correlation between autologous rosetting and activation suggests these may be a subset of activated T lymphocytes. We speculate that the CD2–LFA-3 interaction may help mediate localization and extravasation of activated T lymphocytes at sites of immune reaction. LFA-3 is expressed on endothelial cells (3, 32). Lymphoblasts extravasate throughout the circulation, in contrast to small lymphocytes, which selectively recirculate through high endothelial venules (33). This enhanced adhesion of activated T lymphocytes may explain why the majority of activated T lymphocytes are not found in the circulation but are present in lymph nodes or sites of antigenic stimulation.

Purification of T lymphocytes by sheep E rosetting has been known to cause functional alterations. Larsson et al. (34) found that E rosetting primes T lymphocytes to proliferate in response to lymphokines. Although this is an artificial system, it suggests that interaction of CD2 with the LFA-3 ligand may be a physiologically relevant pathway of T lymphocyte stimulation. Interaction of CD2+ thymocytes with LFA-3+ thymic epithelial cells via CD2/LFA-3 receptor/ligand interactions appears of great importance in functional responses of several different thymocyte subsets (21, 35).

Molecules similar to LFA-3 are present on E in other species. Human T lymphocytes form CD2-dependent rosettes with E from human, sheep, dog, horse, pig, and rabbit (8, 13, 17, 18, 36). Autologous rosetting of thymocytes has been demonstrated in the human, rabbit, rat, and pig (13, 16, 27, 37). A 42 kD surface glycoprotein termed the T11 target structure (T11TS) has been defined on sheep E (38, 39). mAb to T11TS inhibit rosetting of sheep E with either human T cells or sheep T lymphocytes and inhibit a range of T lymphocyte responses in sheep similar to those inhibited by LFA-3 mAb in humans. Furthermore, the purified T11TS molecule competitively inhibits CD2 mAb binding. Comparative studies suggest LFA-3 and T11TS are functional and structural homologues, and the much higher density of T11TS on sheep E than LFA-3 on human E may explain the much more avid rosetting of resting human T cells with sheep than human E (Hüning, T., M. Plunkett, M. Dustin, P. Selvaraj, and T. Springer, unpublished observations). While the significance of the expression of LFA-3 on human E is still not fully appreciated, the conservation of expression of similar structures on E in other mammals that can bind to human CD2 points to its evolutionary importance.

Summary

CD2, also known as LFA-2, T11, and the E rosette receptor, is a T lymphocyte surface protein functionally important in adhesion to target cells and T cell triggering. LFA-3 is a widely distributed cell surface protein that functions in
adhesion on target cells. We find that LFA-3 is expressed on human E, and that CD2 is a receptor for LFA-3 that mediates T cell adhesion to human E. Pretreatment of T lymphocytes with CD2 mAb or of E with LFA-3 mAb inhibits rosetting. Purified CD2 molecules bind to human E and inhibit rosetting. CD2 binding to E is inhibited by LFA-3 mAb; reciprocally, binding of LFA-3 mAb to human E is inhibited by pretreatment with purified CD2. Higher concentrations of CD2 aggregate human E; aggregation is inhibited by mAb to LFA-3.

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