Lymphocyte Function-associated Antigen 1 Dominates Very Late Antigen 4 in Binding of Activated T Cells to Endothelium

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Summary
Lymphocyte function-associated antigen 1/intercellular adhesion molecule 1 (LFA-1/ICAM-1)- and very late antigen 4/vascular cell adhesion molecule 1 (VLA-4/VCAM-1)-mediated adhesion of T lymphocytes to endothelial cells (EC) can be regulated by increased expression of ICAM-1 and VCAM-1 upon cytokine treatment of EC, or by activation of the integrin molecules LFA-1 and VLA-4 on T cells. Here, we provide evidence that preferential usage of LFA-1 over VLA-4 is yet another mechanism to control T cell adhesion. We observed that binding of activated T lymphocytes, as opposed to resting T cells, to EC is essentially mediated through LFA-1 and not through VLA-4. VLA-4-mediated adhesion of T cells to EC is only found when LFA-1 is not expressed or not functional, as observed for several T cell leukemia cell lines. These results suggest that LFA-1-mediated adhesion dominates and may downregulate VLA-4-mediated adhesion through an unidentified mechanism.

Materials and Methods

Adhesion of T lymphocytes to endothelium, lining the blood vessels, is a crucial step in immune surveillance. It allows T lymphocytes to recirculate and migrate into sites of inflammation (1). Different adhesion receptors have been described to be involved in this process (2, 3). The integrins LFA-1 and very late antigen 4 (VLA-4), which are both expressed on T cells, have been reported to mediate binding to endothelial cells (EC) (4-7). One mechanism to regulate adhesion of T lymphocytes to endothelial cells involves activation of EC by inflammatory cytokines such as TNF-α, which results in a rapid increase in the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), ligands of LFA-1 and VLA-4, respectively (3, 8). Recently, the activation state of these integrin molecules expressed by T cells also has been described to play an important role in the regulation of the adhesion function of these cells (9-13). Here we demonstrate that yet another mechanism can regulate cell adhesion. By using an antibody (NKI-L16) that recognizes an activation epitope (termed L16) on LFA-1 (9, 14), we observed that the functional state of the LFA-1 molecule, as reported by this antibody, determines if LFA-1 or VLA-4 is exploited by T cells to bind EC. The results suggest that, only when LFA-1 is not capable to mediate adhesion, VLA-4 is used by T lymphocytes to bind EC, pointing to a selective use of these adhesion receptors by T cells.
as described previously (20). Cells from passages one to three were used for adhesion experiments.

**Clustering Assay.** Binding of T cells to L-ICAM-1 cells was determined by means of double fluorescence. Cells (10⁶/ml) were stained with the green dye sulfofluorescein diacetate (SFDA; Molecular Probes, Junction City, OR) at a concentration of 5 μg/ml or with the red dye Hydroethidine (HE; Polyscience Inc., War- rington, PA) at a concentration of 3 ng/ml, as described previously (9). 10⁶ red-labeled cells and 10⁶ green-labeled cells were incubated at 37°C for different periods of time in Iscove's medium containing 0.5% BSA, and stimulated with PMA (50 ng/ml). Subsequently, cells were fixed with 0.5% (wt/vol) paraformaldehyde, and heterotypic conjugates were measured by FACScan® analysis (Becton Dickinson & Co., Mountain View, CA). Data are representative of four experiments.

**Adhesion Assay.** Human EC were seeded at 2 x 10⁶ cells/ml in FN-coated (2 μg/ml) 96-well plates and were stimulated for 24 h with human rTNF-α (100 U/ml). Adhesion experiments were performed as described previously (20). Briefly, ⁵¹Cr-labeled T cells were allowed to bind at 37°C for 30 min. The number of adherent T cells was quantified in a gamma counter. Results are expressed as the mean percentage of cells binding from triplicate wells. For inhibition studies, cells were preincubated (30 min, 4°C with 1:100 ascites dilution or 10 μg/ml purified mAb. Data are representative for four experiments. For adhesion experiments to VCAM-1, purified soluble VCAM-1 (21) (0.8 μg/ml) was coated for 16 h at 4°C. Subsequently, wells were coated by 1% (wt/vol) BSA for 1 h at 37°C. T cell adhesion was performed under the same conditions as described for EC.

**Immunofluorescence.** Cells were incubated for 30 min at 4°C in PBS, 0.5% (wt/vol) BSA, 0.2% azide with appropriate dilutions of the mAb, followed by incubation with FITC-labeled goat (Fab') anti-mouse IgG antibody (GAM-FITC; Nordic, Tilburg, the Netherlands) for 30 min at 4°C. The relative fluorescence intensity was measured by FACScan® analysis (Becton Dickinson and Co.).

## Table 1. Expression of Cell Adhesion Molecules on Different T Cells and Endothelial Cells

| mAb          | Antigen | JS136 | Ly | Ly IL-2 | Jurkat | CEM | LAD 6.6 | Cultured endothelial cells |
|--------------|---------|-------|----|---------|--------|-----|---------|--------------------------|
|              |         |       |    |         |        |     |         | Medium | 24 h TNF-α |
| GAM-FITC     | Control | 2     | 1  | 1       | 2      | 3   | 3       | 2       | 4           |
| SPV-L7       | LFA-1   | 307   | 44 | 42      | 40     | 31  | 4       | 1       | 1           |
| NKI-L16      | LFA-1*  | 304   | 19 | 31      | 3      | 5   | 3       | 2       | 3           |
| HP 2/1       | VLA-4   | 74    | 41 | 30      | 23     | 46  | 130     | 1       | 1           |
| F10.2        | ICAM-1  | 40    | 5  | 21      | 16     | 14  | 29      | 44      | 394         |
| 4B9          | VCAM-1  | 2     | 2  | 3       | 3      | 2   | 3       | 4       | 73          |
| ENA-1        | ELAM-1  | 3     | 6  | 5       | 4      | 4   | 4       | 6       | 14          |

Lymphocytes (Ly) were freshly isolated or cultured for 24 h with 100 U/ml IL-2 (Ly IL-2). The LFA-1+ and LFA-1- T cell clones JS136 and LAD6.6, respectively, and the T cell lines Jurkat and CEM were cultured as described in Materials and Methods. The EC were activated by culturing for 24 h in the presence of 100 U/ml TNF-α. Antigen expression was determined by immunofluorescence. One representative experiment out of four is shown.

* Ca²⁺-dependent epitope.

**Results and Discussion**

The contribution of the LFA-1/ICAM-1 and VLA-4/VCAM-1 adhesion receptor pairs in T cell–EC interactions was examined by binding of resting and activated T cells to 24-h TNF-α-cultured EC, which expressed high levels of ICAM-1 and VCAM-1, and only low levels of ELAM-1 (Table 1). LFA-1+ T cells (JS136, PBL, CEM, and Jurkat) as well as LFA-1- T cells (LAD 6.6), obtained from a patient suffering the LAD syndrome (19), showed significant binding to TNF-α-stimulated EC (Fig. 1 A). Interestingly, we observed that, although approximately equal numbers of the different cell types bound to EC (except resting PBL), distinct receptor pairs were used to mediate adhesion. T cell clone JS136 and IL-2-cultured lymphocytes showed LFA-1-restricted adhesion (blocked by anti-CD18 antibodies; Fig. 1 B). In contrast, the LFA-1- T cell clone (LAD 6.6) and two LFA-1- T cell lines (CEM and Jurkat) bound to TNF-α-EC exclusively through VLA-4 (Fig. 1 B). Compared with the cultured T cells, binding of freshly isolated lymphocytes to TNF-α-stimulated EC was significantly lower (Fig. 1 A) and was mediated both by LFA-1 and VLA-4 (Fig. 1 B). Antibodies directed against ICAM-1 and VCAM-1 blocked the adhesion of the cells to the same extent as anti-LFA-1 or anti-VLA-4 antibodies, respectively (not shown). Antibodies to ELAM-1 did not block the adhesion, indicating that ELAM-1 is not involved in this process (not shown; 20). These results indicate that only resting PBL use both adhesion pathways (LFA-1/ICAM-1 and VLA-4/VCAM-1). Upon in vitro culture of PBL there is a tendency towards LFA-1-dependent/VLA-4-independent adhesion, whereas fully activated T cells, like a T cell clone (several other T cell clones were studied; not shown), exclusively use LFA-1 but not VLA-4. In con-
contrast to this shift from LFA-1/VLA-4-mediated adhesion to only LFA-1-mediated adhesion, we observed that several leukemic T cell lines that express significant levels of LFA-1 (Table 1) bind EC exclusively through VLA-4. In all cases adhesion of T cells to TNF-α-stimulated EC could not be blocked completely by anti-LFA-1 and anti-VLA-4 antibodies (up to 60–80% of total adhesion; Fig. 1 C), indicating that other as yet undefined adhesion structures mediate the remaining 20–40% of adhesion.

The selective use of LFA-1 or VLA-4 by T cells to mediate adhesion to EC prompted us to investigate the expression of these adhesion receptors in more detail (Table 1). All T cells expressed significant levels of VLA-4, indicating that in principle all cells are capable of using VLA-4 to mediate adhesion to TNF-α-stimulated EC. As expected, LFA-1 expression is totally absent on LAD T cells (LAD 6.6), thus explaining the VLA-4-mediated binding to TNF-α-stimulated EC. However, all other T cells expressed significant levels of LFA-1 (JS136, lymphocytes, CEM, and Jurkat). LFA-1 is expressed at much higher levels on JS136 compared with PBL, CEM, and Jurkat. Interestingly, we observed that expression of the L16 activation epitope, a Ca2+-dependent epitope on LFA-1, which recognizes a “potentially active” form of LFA-1 (9), is absent on the LFA-1+ CEM and Jurkat T cells, whereas expression is low on resting lymphocytes (9) and high on IL-2-cultured lymphocytes and on T cell clone JS136. Earlier work indicated that expression of the L16 epitope is a prerequisite for LFA-1 to mediate cell adhesion (9, 14). This finding suggests that JS136 and IL-2-cultured PBL express a form of LFA-1 that can readily be activated to high-avidity ligand binding, whereas LFA-1 expressed by CEM and Jurkat cells lacks L16 expression and can therefore not reach its activated state, thus explaining their LFA-1-independent, VLA-4-mediated adhesion to TNF-α-stimulated EC. The dull expression of the L16 epitope on resting lymphocytes correlates with the observation that the interaction of resting PBL is only partially mediated by LFA-1 since only a small number of the expressed LFA-1 molecules can become activated.

To determine the functional activity of the LFA-1 adhesion receptors expressed on these T cells, we examined the capacity of these T cells to bind L cell transfectants expressing ICAM-1 (Fig. 2). It is known that LFA-1-mediated adhesion can be induced by the addition of PMA to T cells, resulting in high-avidity ligand binding (22). The LFA-1- T cells (LAD 6.6), which were used as a control, could not bind to L-ICAM-1 (Fig. 2). As expected, binding of L16+ JS136 T cells and lymphocytes to L-ICAM-1 cells was induced upon addition of PMA, and could be blocked completely to background levels by anti-CD18 or anti-CD54 antibodies (not shown). In contrast, addition of PMA to the LFA-1+ T cells (CEM and Jurkat) did not result in activation of LFA-1, because no binding to L-ICAM-1 cells was observed. To exclude the possibility that this was caused by the relatively low expression of LFA-1 on these cells (compared with JS136), we determined the binding capacity of PBL that were briefly cultured in IL-2 to express approximately similar levels of LFA-1 as Jurkat and CEM. In contrast to the latter two cell lines,
these L16⁺ lymphocytes could readily be induced by PMA to bind L-ICAM-1, demonstrating that the level of LFA-1 expression is not limiting. Also, other stimuli known to activate LFA-1 (anti-CD2, -CD3, or the addition of Mn²⁺ ; 9, 11, 23) were incapable of inducing the activated state of the LFA-1 receptor on Jurkat and CEM T cells (not shown).

The results from this study demonstrate that the selective use of adhesion receptors in adhesion and migration of T cells into sites of inflammation is not only regulated by an increased expression of the adhesion receptors' ligands ICAM-1 and VCAM-1 by inflammatory cytokines, such as TNF-α, but is also dependent on the activated state of the adhesion receptor itself, expressed on the T cell. Expression of the Ca²⁺-dependent L16 epitope on LFA-1 determines if the LFA-1 adhesion receptor is in a "potentially active" state. Because L16 is a Ca²⁺-dependent epitope, Ca²⁺ cations may play an important role in the formation of this conformation of LFA-1 (9). If LFA-1 expressed on T cells lacks the L16 epitope, it cannot be triggered to create a high affinity ligand binding form. To circumvent this defect these cells may use the VLA-4 receptor VCAM-1 interaction as an alternative adhesion route, which is used by the LFA-1⁺ T cells, as well as the Jurkat and CEM T cells. On the other hand, if LFA-1 on T cells expresses the L16 epitope, LFA-1 mediates adhesion to endothelium, without any contribution of VLA-4 (Fig. 1). It is tempting to speculate that when the LFA-1/ICAM-1 interaction takes place, the VLA-4/VCAM-1 contribution in T cell/TNF-α-EC interaction is downregulated through an unknown mechanism. Work is in progress to test this hypothesis.

To exclude the possibility that VLA-4 expressed on JS136 is defective, and therefore not able to mediate adhesion to its ligands, we determined the capacity of VLA-4, expressed by these different T cells, to bind VCAM-1, a ligand of VLA-4 (24) (Fig. 3). VLA-4 can be activated to bind VCAM-1 by the addition of PMA or by specific anti-β1 antibodies that induce the high affinity state of VLA-4, resulting in enhanced binding of VLA-4 to VCAM-1 and/or FN (10, 12, 13). Despite the fact that VLA-4 was not equally expressed on all T cells (Table 1), all T cells used in this study (LFA-1⁺/L16⁺, LFA-1⁺/L16⁻, and LFA-1⁻) could be induced by an anti-β1 antibody (TS2/16; 10) or by PMA (data not shown) to bind to VCAM-1 or FN (data not shown). This induced interaction was completely VLA-4 mediated, since anti-VLA-4 antibodies blocked the interaction. These data indicate that in contrast to LFA-1, the VLA-4 receptor on all T cells used in this study can become active to bind VCAM-1. Moreover, binding of JS136 T cells to TNF-α-stimulated EC also can be enhanced by anti-β1 antibodies (10). Although the increase in the total number of cells bound is limited (from 50 to 60%), this is associated with a clear shift from LFA-1-mediated adhesion to a VLA-4/VCAM-1-mediated adhesion to EC (Fig. 4). However, if both LFA-1 and VLA-4 are activated through the addition of PMA, JS136 T cells primarily use LFA-1 and not VLA-4 to bind EC, indicating that the LFA-1 molecule, when activated, dominates VLA-4 in T cell-EC interaction (Fig. 4). The addition of PMA to CEM
or Jurkat T cells did not alter the VLA-4-dependent adhesion to EC into a LFA-1-dependent adhesion, providing further evidence that their LFA-1 molecules are not functional (not shown).

It should be noted that binding of T cells to isolated ligands (ICAM-1, VCAM-1, and FN) or ligands expressed by transfected L cells is low unless the T cells are activated by PMA or other stimuli, inducing a high affinity state of the integrin receptor (9, 13, 25). Nevertheless, we consistently observed strong binding of the cells used in this study to EC via these ligands (ICAM-1 and VCAM-1). This suggests that other interactions precede engagement of LFA-1 or VLA-4, as has been demonstrated for ELAM-1 (26). It can be excluded that E-selectin and L-selectin are involved in this process (26, 27). Activated T cells lack L-selectin expression, whereas E-selectin expression is low on EC after prolonged (24-h) exposure to TNF-α (Table 1). This indicates that other, undefined molecules expressed by these T cells may induce high affinity binding of VLA-4 or LFA-1 upon binding of TNF-α-stimulated EC. One possible candidate is CD31, which has recently been described to stimulate β1- and β2-mediated adhesion of T cell subsets to VCAM-1 and ICAM-1 (28). CD31 seems to preferentially stimulate β1-mediated adhesion, whereas in our study, β2-mediated adhesion seems to dominate β1-mediated adhesion, suggesting that also other molecules may be involved.

Since transendothelial migration of T cells mainly involves the LFA-1/ICAM-1 interaction (29), and not the VLA-4/VCAM-1 interaction, the absence of the L16 epitope on LFA-1 can have serious effects on the transendothelial migration capacity of LFA-1-L16 T cells. Indeed, it has been reported that migration of LFA-1- (LAD) T cells through EC is severely affected by the absence of LFA-1 (30). We therefore assume that LFA-1+ T cells, which lack the L16 epitope, show binding to EC using VLA-4, but migrate poorly through EC. In contrast, LFA-1+L16+ T cells will readily bind EC, and migrate through EC using high affinity LFA-1. This may provide the immune system with a mechanism by which preferentially activated LFA-1-L16+ T cells will be capable of migrating into tissues and actively participating in the effector phase of an inflammatory/immune response.

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