Very Late Antigen 4-dependent Adhesion and Costimulation of Resting Human T Cells by the Bacterial β1 Integrin Ligand Invasin

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Summary

Bacteria and viruses often use the normal biological properties of host adhesion molecules to infect relevant host cells. The outer membrane bacterial protein invasin mediates the attachment of Yersinia pseudotuberculosis to human cells. In vitro studies have shown that four members of the very late antigen (VLA) integrin family of adhesion molecules, VLA-3, VLA-4, VLA-5, and VLA-6, can bind to invasin. Since CD4+ T cells express and use these integrins, we have investigated the interaction of CD4+ T cells with purified invasin. Although VLA integrin-mediated adhesion of T cells to other ligands such as fibronectin does not occur at high levels unless the T cells are activated, resting T cells bind strongly to purified invasin. The binding of resting T cells to invasin requires metabolic activity and an intact cytoskeleton. Although CD4+ T cells express VLA-3, VLA-4, VLA-5, and VLA-6, monoclonal antibody (mAb) blocking studies implicate only VLA-4 as a T cell invasin receptor. Like other integrin ligands, invasin can facilitate T cell proliferative responses induced by a CD3-specific mAb. These results suggest that the nature of the integrin ligand is a critical additional factor that regulates T cell integrin activity, and that direct interactions of T cells with bacterial pathogens such as Yersinia may be relevant to host immune responses to bacterial infection.

The immune response is dependent on the physical interaction of its various cellular members with each other and with the surrounding microenvironment (1). Integrins are a large family of α/β heterodimeric proteins that mediate the adhesion of many different cell types to each other and to components of the extracellular matrix (ECM) such as fibronectin (FN), laminin, and collagen (1–3). Since T cells must be able to rapidly alternate between adhesive and nonadhesive states, the functional activity of integrins expressed on T cells is tightly regulated. T cell activation rapidly modulates the functional activity of four integrins expressed on peripheral T cells: the β2 integrin LFA-1 and the β1 integrins very late antigen (VLA)-4 (also designated α4β1), VLA-5 (α5β1), and VLA-6 (α6β1). Whereas resting T cells demonstrate minimal integrin-mediated adhesion, activation results within minutes in strong T cell adhesion to integrin ligands without a change in the level of cell surface expression of the integrin receptors themselves (4–6). Multiple activation signals can induce this rapid change in integrin activity, including treatment with the phorbol ester PMA, the Ca2+ ionophore A23187, mitogenic pairs of CD2-specific mAbs, mAb cross-linking of the CD3-TCR complex, or mAb cross-linking of the T cell surface molecules CD7, CD28, or CD31 (4–8). To date, this dependence on activation for strong T cell integrin function has been demonstrated for all of the integrin ligands tested, including the LFA-1 ligand intercellular adhesion molecule 1 (ICAM-1), the VLA-4 cell surface ligand vascular cell adhesion molecule (VCAM)-1, the VLA-4 and VLA-5 ligand FN, and the VLA-6 ligand laminin (4–7, 9).

Whereas adhesion molecules play a fundamentally critical role in immune system function, their adhesive properties are often used by bacteria and viruses as a means of entry and survival in the host organism (10, 11). Recent studies of the intracellular bacterial pathogen Yersinia pseudotuberculosis have shown that the bacterial outer membrane protein invasin mediates the attachment and internalization of Yersinia by normally nonphagocytic cells by binding to four different VLA integrins: VLA-3, VLA-4, VLA-5, and VLA-6 (12, 13). Since CD4+ T cells express all of these VLA integrins (6), and VLA-4 in particular is expressed predominantly by lymphoid cells (2), we hypothesized that the interaction of T cells with invasin may be critical to our understanding of integrin function and immune responses to this bacterial pathogen. We show in this study that: (a) strong T cell binding to invasin occurs without activation, unlike binding to all
other T cell integrin ligands tested to date; (b) the predominant invasin receptor on CD4+ T cells is VLA-4; and (c) invasin can facilitate CD3-mediated T cell proliferative responses.

Materials and Methods

**Human T Cells.** Peripheral CD4+ T cells were isolated by negative magnetic immunoselection from either leukapheresis packs or buffy coats as previously described (6, 7, 14). The T cell populations were typically >96% CD3+CD4+ as assessed by flow cytometric analysis. Complete depletion of monocytes in the T cell preparation was determined by the lack of proliferative response to optimal concentrations (1:200 dilution) of PHA (M form) (Gibco-BRL, Grand Island, NY).

**Antibodies and Other Reagents.** The following mAbs were used as purified IgG: anti-CD3 mAb OKT3, anti-CD7 mAb 3A1, and anti-LFA-1 a chain mAb TS1/22 (American Type Culture Collection, Rockville, MD); anti-VLA-5 a chain mAb MAB16 (15) and anti-VLA-B chain mAb MAB13 (15) (provided by Dr. K. Yamada, National Institutes of Health [NIH], Bethesda, MD); and anti-VLA-4 a chain mAb NIH49d-1 (8) (Drs. S. Shaw and Y. Tanaka, NIH). The following mAbs were used as dilutions of ascites fluid: anti-CD28 mAb 9.3 (J. Ledbetter, Bristol Myers Squibb, Seattle, WA); anti-CD2 mAbs 95-5-49 and 9-1 (Dr. R Dupont, Memorial Sloan Kettering Cancer Center, New York, NY); anti-VLA-3 a chain mAb PI85, anti-VLA-5 a chain mAb P1D6, and anti-VLA-4 a chain mAb P4G9 (Telios Pharmaceuticals, Inc., San Diego, CA); and anti-VLA-4 a chain mAb L25 (16) (Dr. P. Estess, Becton Dickinson & Co., Mountain View, CA). The following mAbs were used as dilutions of culture supernatant: anti-VLA-6 a chain mAb GoH-3 (Dr. A. Sonnenberg, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands); anti-VLA-5 a chain mAbs BII12 and B1E5, and anti-VLA-B chain mAb AII82 (Dr. C. Damsky, University of California, San Francisco, CA); the anti-VLA-4 a chain mAbs HP2/1, HP1/2, HP2/4, HP1/1, HP1/7 (17), and the anti-VLA-B chain mAbs LIA1/2, ALEX1/4, LIA1/5, and TS2/16 (18) (kindly provided by Dr. F. Sanchez-Madrid, Universidad Autonoma de Madrid, Madrid, Spain).

The invasin utilized in this study is a fusion protein consisting of the COOH-terminal end of invasin (479 amino acids in length) and maltose binding protein (MBP) (13). MBP and collagen (Sigma Chemical Co., St. Louis, MO) were used as negative control proteins. FN was purchased from the New York Blood Center (New York, NY). Cytochalasin B was purchased from Sigma Chemical Co., and staurosporin was purchased from Boehringer Mannheim Diagnostics (Indianapolis, IN). Both were dissolved in DMSO before use. Dibutyryl cAMP (Calbiochem-Behring Corp., San Diego, CA) was dissolved in PBS before use.

**Adhesion Assays.** Adhesion assays were performed as described (6, 7). Each well contained 50,000 3HCr-labeled T cells in a final volume of 0.1 ml PBS/0.5% HSA. For PMA activation, cells were added to wells containing 10 ng/ml PMA (Sigma Chemical Co.). All data are expressed as the mean percent of cells binding from three replicate wells plus SEM. In all mAb blocking experiments, mAbs were added to wells at 10 ng/ml (for purified IgG), 1:500 dilution (for ascites fluid) or 1:5 dilution (for culture supernatants). Inhibitors were present throughout the assay at the concentrations indicated.

**T Cell Proliferation Assays.** Proliferation assays were performed essentially as previously described (19). During the last 18 h of the assay, the culture was pulsed with 1 μCi/well of [3H]thymidine (New England Nuclear/Dupont, sp act of 6.7 Ci/mmol). Results are expressed as the arithmetic mean cpm of triplicate cultures. Microtiter plates (Costar Corp., Cambridge, MA) were prepared by first incubating indicated concentrations of the CD3 mAb OKT3 overnight at 4°C in PBS, washing away the unbound mAb, and adding the indicated concentrations of invasin or FN (diluted in PBS with Ca2+ and Mg2+) for an addition 2-3 h incubation at room temperature. Plates were washed three times with PBS before the start of culture. mAbs were added at the same concentrations used in the adhesion assays, except for culture supernatants, which were used at a 1:8 final dilution.

**Results**

**Binding of Resting As Well As Activated T Cells To Purified Invasion.** Previous studies have shown that strong adhesion of human CD4+ T cells to relevant VLA ligands such as FN (via VLA-4 and VLA-5), laminin (via VLA-6), and VCAM-1 (via VLA-4) requires activation of the T cell by a stimulus such as PMA (6, 7, 9). In contrast to the results obtained with these previously described VLA integrin ligands, resting CD4+ T cells bound strongly and in a dose-dependent fashion to purified invasin (Fig. 1). Treatment of T cells for 10 min with 10 ng/ml PMA dramatically increased adhesion to FN, but only slightly increased adhesion to invasin (Fig. 1). An increase in binding to invasin after PMA activation of T cells was most evident at low doses of immobilized invasin. Similar results were obtained after activation of T cells with other stimuli that increase VLA integrin-mediated binding to FN (6, 7, and data not shown).

**VLA-4 Is the Predominant Integrin Invasin Receptor on Human T Cells.** mAb blocking studies were performed using a large panel of VLA-B chain- and VLA a chain-specific mAbs. The data in Fig. 2 show that the VLA-B chain-specific mAb AII82, which has previously been shown to block the binding

*Figure 1.* Binding of resting and PMA-activated CD4+ T cells to purified invasin. Binding of 3HCr-labeled CD4+ T cells to purified invasin, MBP, or FN (applied at the indicated concentrations) after no activation (open squares) or after activation for 10 min at 37°C with 10 ng/ml PMA (solid squares). Binding of resting and PMA-activated T cells to collagen was <3%. Data are representative of a minimum of four experiments with different donors.
of the erythroleukemia cell line K562 to invasin (12), can also completely inhibit T cell adhesion to invasin. In addition, two other VLA β chain–specific mAbs, LIA1/2 and MAB13, can inhibit T cell adhesion to invasin. Three other VLA β chain–specific mAbs only partially inhibit T cell adhesion to invasin, suggesting that these mAbs recognize epitopes on the VLA β chain that are minimally involved in binding to invasin.

Studies with various VLA α chain–specific mAbs demonstrate that one VLA-4 α chain–specific mAb, HP1/2, can inhibit T cell adhesion to invasin as effectively as the inhibitory VLA β chain–specific mAbs (Fig. 2). A panel of VLA-5 α chain–specific mAbs, all of which inhibit cell adhesion to FN, did not inhibit T cell adhesion to invasin. This panel includes one VLA-5-specific mAb (BIIG2) that was previously shown to inhibit the binding of K562 cells to invasin (12). In addition, the VLA-3 α chain–specific mAb P1B5 and the VLA-6 α chain–specific mAb GoH-3, both of which are functionally inhibitory mAbs (6, 20, and Y. Shimizu, unpublished results), did not inhibit T cell adhesion to invasin. Thus, these data strongly suggest that VLA-4 is the predominant invasin receptor on human T cells.

**Binding of Resting T Cells to Invasin Requires Metabolic Activity and an Intact Cytoskeleton.** We assessed the ability of various metabolic inhibitors to inhibit the binding of resting T cells to invasin as a first test of whether engagement by invasin generates intracellular signals that might rapidly upregulate VLA integrin activity. The data in Fig. 3 demonstrate that the increased adhesion to invasin observed with PMA-activated T cells can be inhibited to the level of resting T cell binding by the protein kinase C (PKC) inhibitor staurosporin. However, staurosporin did not inhibit resting T cell adhesion to invasin, suggesting that adhesion of resting T cells to invasin is not dependent on PKC activation. Treatment of T cells with the cAMP analogue dibutyryl cAMP, which has been shown to inhibit activation-dependent T cell adhesion to FN and ICAM-1 (4, 7), or the tyrosine kinase inhibitor herbimycin A also did not inhibit the binding of resting T cells to invasin (Fig. 3 and data not shown). However, treatment of T cells with sodium azide significantly inhibited invasin binding by resting T cells, suggesting that T cell adhesion to invasin requires a metabolically active T cell. Furthermore, the ability of the cytoskeletal disrupting agent cytochalasin B to inhibit the binding of both resting and PMA-activated T cells to invasin is consistent with earlier data implicating the cytoskeleton in integrin-mediated adhesive events (21). Treatment of T cells with EDTA also abolishes T cell binding to invasin, consistent with the divalent cation requirements of integrin receptors.

**Invasin Facilitates CD3-mediated T Cell Proliferation.** The interaction of VLA integrins with a relevant ligand can also facilitate T cell proliferative responses. This has been most effectively demonstrated in an in vitro system where purified
T cells are activated through the CD3–TCR by the CD3-specific mAb OKT3 immobilized on plastic. In the absence of accessory cells, human T cells fail to proliferate in response to immobilized CD3 mAb alone (9, 19). However, vigorous T cell proliferation occurs when a VLA integrin ligand, such as FN, laminin, or VCAM-1, is coimmobilized with the CD3 mAb (9, 15, 19, 22). Fig. 4 shows that as with other VLA integrin ligands, coimmobilization of invasin with the CD3 mAb OKT3 can also result in T cell proliferation. The same VLA4 α chain– and VLA β chain–specific mAbs that inhibit T cell adhesion to invasin (Fig. 2) also inhibit T cell proliferation induced by coimmobilized invasin and CD3 mAb (data not shown).

Discussion

We have shown in this study that human CD4+ T cells bind via VLA integrins to the bacterial protein invasin. However, unlike other VLA integrin ligands, there is strong adhesion of resting T cells to invasin with a relatively small increase in the overall strength of adhesion after modes of activation that dramatically increase T cell adhesion to other integrin ligands such as FN, VCAM-1, and laminin. Thus, these findings illustrate an important additional regulatory component to integrin receptors. Other properties common to integrin ligands, such as the ability to facilitate CD3-mediated T cell proliferative responses (Fig. 4), are also exhibited by invasin.

The exact mechanism by which invasin promotes such vigorous adhesion of resting T cells to invasin currently remains undefined. One possibility is that the high affinity of invasin for its VLA integrin receptors can overcome the low functional activity of VLA integrins on resting T cells. This mechanism would suggest that any integrin ligand with sufficiently high affinity would be able to mediate the adhesion of resting T cells. A second possibility is that binding of resting T cells to invasin results in the generation of a signal that upregulates VLA integrin activity. This hypothesis is supported indirectly by: (a) the requirement for a metabolically active T cell to observe binding to invasin (Fig. 3); and (b) numerous reports of mAbs directed against the VLA-4 α chain or the VLA-6 chain that can upregulate adhesion to relevant ligands (17, 18, 23–25). We are continuing to investigate the potential of invasin as an integrin regulatory molecule. Nevertheless, our results clearly illustrate that in addition to the already well established role of activation in regulating T cell integrin function, the nature of the ligand itself also plays an important role in regulating adhesion. Thus, integrin-mediated adhesion to distinct ligands can be regulated in very different ways.

mAb blocking studies indicate that the VLA-4 integrin is the predominant invasin receptor on CD4+ T cells (Fig. 2). Even though CD4+ T cells express VLA-3, VLA-5, and VLA-6, and these VLA integrins have previously been shown to bind to invasin (12), we were unable to identify any mAbs specific for VLA-3, VLA-5, or VLA-6 that were able to inhibit T cell binding to invasin. This may be due to the higher levels of VLA-4 expressed on CD4+ T cells compared with VLA-3, VLA-5, and VLA-6 (6). However, the contribution of specific VLA integrins to adhesion to a specific ligand does not always correlate with the level of integrin expression. For example, T cell adhesion to FN is mediated predominantly by VLA-5, even though it is expressed at lower levels on T cells than VLA-4, which also binds FN (6). There may also be cell type-specific differences in the ligand specificity of individual VLA integrins since VLA-2 has been shown to differentially recognize laminin depending upon the specific type of cell in which VLA-2 is expressed (26). Thus, it is conceivable that VLA-3, VLA-5, and VLA-6 on human T cells do not function as invasin receptors as they do on other cell types that express these receptors. The inability of the VLA-5-specific mAb BIIG2 to inhibit T cell binding to invasin is consistent with this hypothesis, since this mAb was previously shown to inhibit the binding of K562 cells to invasin (12).

Although enteropathogenic bacteria such as Yersinia are thought to mainly interact with epithelial and other connective tissue cells, T cell interactions with bacteria may also be relevant to our understanding of bacterial pathogenicity. Our results suggest that invasin allows Yersinia to potentially interact with any human cells that express the appropriate VLA integrins, even cells that normally express these receptors in a low activity functional state. This strategy allows invasin-bearing bacteria to overcome the normal mechanisms that regulate integrin functional activity. The ability of invasin to facilitate CD3-mediated T cell proliferation (Fig. 4) suggests that Yersinia might also be able to modulate the imo...
immune response in vivo by VLA integrin-mediated interactions with invasin. Our data, coupled with other indirect lines of evidence such as localization of Yersinia to anatomic sites rich in T cells such as Peyer’s patches (27) and the isolation of Yersinia-specific T cell clones (28), suggest that further investigation of the significance of lymphocyte interactions with bacterial pathogens is warranted.

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References

1. Springer, T.A. 1990. Adhesion receptors of the immune system. Nature (Lond.). 346:425.
2. Hemler, M.E. 1990. VLA proteins in the integrin family: structures, functions, and their role on leukocytes. Annu. Rev. Immunol. 8:365.
3. Shimizu, Y., and S. Shaw. 1991. Lymphocyte interactions with extracellular matrix. PASEB (Fed. Am. Soc. Exp Biol.) J. 5:2292.
4. Dustin, M.L., and T.A. Springer. 1989. T-cell receptor cross-linking transiently stimulates adhesiveness through LFA-1. Nature (Lond.). 341:619.
5. van Kooyk, Y., P. van de Wiel-van Kemenade, P. Weder, T.W. Kuiljpers, and C.G. Figdor. 1989. Enhancement of LFA-1-mediated cell adhesion by triggering through CD2 or CD3 on T lymphocytes. Nature (Lond.). 342:811.
6. Shimizu, Y., G.A. van Seventer, K.J. Horgan, and S. Shaw. 1990. Regulated expression and function of three VLA (β1) integrin receptors on T cells. Nature (Lond.). 345:250.
7. Shimizu, Y., G.A. van Seventer, E. Ennis, W. Newman, K.J. Horgan, and S. Shaw. 1992. Crosslinking of the T cell-specific accessory molecules CD7 and CD28 modulates T cell adhesion. J. Exp. Med. 175:577.
8. Tanaka, Y., S.M. Albelda, K.J. Horgan, G.A. van Seventer, Y. Shimizu, W. Newman, J. Hallam, P.J. Newman, C.A. Buck, and S. Shaw. 1992. CD31 expressed on distinctive T cell subsets is a preferential amplifier of β1 integrin-mediated adhesion. J. Exp. Med. 176:245.
9. van Seventer, G.A., W. Newman, Y. Shimizu, T.B. Nutman, Y. Tanaka, K.J. Horgan, T.V. Gopal, E. Ennis, D. O’Sullivan, H. Grey, and S. Shaw. 1991. Analysis of T cell stimulation by superantigen plus major histocompatibility complex class II molecules or by CD3 monoclonal antibody: costimulation by purified adhesion ligands VCAM-1, ICAM-1, but not ELAM-1. J. Exp. Med. 174:901.
10. Falkow, S. 1991. Bacterial entry into eukaryotic cells. Cell. 65:1099.
11. Isberg, R.R. 1991. Discrimination between intracellular uptake and surface adhesion of bacterial pathogens. Science (Wash. DC). 252:934.
12. Isberg, R.R., and J.M. Leong. 1990. Multiple β1 chain integrins are receptors for invasin, a protein that promotes bacterial penetration into mammalian cells. Cell. 60:861.
13. Leong, J.M., R.S. Fournier, and R.R. Isberg. 1990. Identification of the integrin-binding domain of the Yersinia pseudotuberculosis invasin protein. EMBO (Eur. Mol. Biol. Organ.) J. 9:1797.
14. Horgan, K.J., and S. Shaw. 1991. Immunomagnetic negative selection of lymphocyte subsets. In Current Protocols in Immunology. J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, and W. Strober, editors. John Wiley and Sons, New York. 7.4.1-7.4.6.
15. Matsuyama, T., A. Yamada, J. Kay, K.M. Yamada, S.K. Akiyama, S.P. Schlossman, and C. Morimoto. 1989. Activation of CD4 cells by fibronectin and anti-CD3 antibody. A synergistic effect mediated by the VLA-5 fibronectin receptor complex. J. Exp. Med. 170:1135.
16. McIntyre, BW., E.L. Evans, and J.L. Bednarczyk. 1989. Lymphoneocyte surface antigen L25 is a member of the integrin receptor superfamily. J. Biol. Chem. 264:13745.
17. Pulido, R., M.J. Elices, M.R. Campanero, L. Osborn, S. Schiffer, A. Garcia-Pardo, R. Lobb, M.E. Hemler, and F. Sanchez-Madrid. 1991. Functional evidence for three distinct and independently inhibitable adhesion activities mediated by the human integrin VLA-4. Correlation with distinct α4 epitopes. J. Biol. Chem. 266:10241.
18. Arroyo, A.G. P. Sanchez-Mateos, M.R. Campanero, I. Martin-Padura, E. Dejana, and F. Sanchez-Madrid. 1992. Regulation of the VLA integrin-ligand interactions through the β1 subunit. J. Cell Biol. 117:659.
19. Shimizu, Y., G.A. van Seventer, K.J. Horgan, and S. Shaw. 1990. Costimulation of proliferative responses of resting CD4+ T cells by the interaction of VLA-4 and VLA-5 with fibronectin or VLA-6 with laminin. J. Immunol. 145:659.
20. Sonnenberg, A., P.W. Modderman, and F. Hogervorst. 1988. Laminin receptor on platelets is the integrin VLA-6. Nature
21. Horwitz, A., K. Duggan, C. Buck, M.C. Beckerle, and D. Burridge. 1986. Interaction of plasma membrane fibronectin receptor with talin-a transmembrane linkage. Nature (Lond.). 320:531.

22. Davis, L.S., N. Oppenheimer-Marks, J.L. Bednarczyk, B.W. McIntyre, and P.E. Lipsky. 1990. Fibronectin promotes proliferation of naive and memory T cells by signaling through both VLA-4 and VLA-5 integrin molecules. J. Immunol. 145:785.

23. Van de Wiel-van Kememade, E., Y. Van Kooyk, A.J. De Boer, R.J.F. Huijbens, P. Weder, W. Van de Kastelee, C.J.M. Melief, C.G. Figdor. 1992. Adhesion of T and B lymphocytes to extracellular matrix and endothelial cells can be regulated through the \( \beta \) subunit of VLA. J. Cell Biol. 117:461.

24. Campanero, M.R., R. Pulido, M.A. Urra, M. Rodriguez-Moya, M.O. De Landazuri, and F. Sanchez-Madrid. 1990. An alternative leukocyte homotypic adhesion mechanism, LFA-1/ICAM-1 independent, triggered through the human VLA-4 integrin. J. Cell Biol. 110:2157.

25. Bednarczyk, J.L., and B.W. McIntyre. 1990. A monoclonal antibody to VLA-4 \( \alpha \)-chain (CDw49d) induces homotypic lymphocyte aggregation. J. Immunol. 144:777.

26. Elices, M.J., and M.E. Hemler. 1989. The human integrin VLA-2 is a collagen receptor on some cells and a collagen-laminin receptor on others. Proc. Natl. Acad. Sci. USA. 86:9906.

27. Une, T. 1977. Studies on the pathogenicity of Yersinia enterocolitica: III. Comparative studies between Y. enterocolitica and Y. pseudotuberculosis. Microbiol. Immunol. 21:505.

28. Autenrieth, I.B., A. Tingle, A. Reske-Kunz, and J. Heesemann. 1992. T lymphocytes mediate protection against Yersinia enterocolitica in mice: characterization of murine T-cell clones specific for Y. enterocolitica. Infect. Immun. 60:1140.