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Integrin-Dependent Role of Human T Cell Matrix Metalloproteinase Activity in Chemotaxis Through a Model Basement Membrane

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Abstract Human T lymphoblastoma cells of the $CD4^+$ 8^+ Tsup-1 line, that express alpha4 and alpha5 but not alpha6 integrins of the beta1 family, and $CD4^+$ human blood T cells bind vasoactive intestinal peptide (VIP) with high affinity, leading to increased adherence, secretion of matrix metalloproteinases (MMPs), and chemotaxis. VIP-enhanced adherence of T cells to fibronectin was inhibited significantly by neutralizing monoclonal antibodies to beta1 > alpha4 >> alpha5, but not to alpha6. Antibodies to beta1 and alpha4 suppressed to a similarly significant extent VIP stimulation of both MMP-dependent T cell chemotaxis through fibronectin-enriched Matrigel and T cell degradation of ^{3}H-type IV collagen in the Matrigel, without affecting VIP-evoked secretion of MMP by suspensions of T cells. The lesser inhibition of VIP-enhanced adherence of T cells to fibronectin by anti-alpha5 antibody, than antibodies to beta1 or alpha4 chains, was associated with lesser or no suppression of MMP-dependent T cell chemotaxis through Matrigel and T cell degradation of type IV collagen in the Matrigel in response to VIP. Specific beta1 integrins thus mediate interactions of stimulated T cells with basement membranes, including adherence, localized digestion by MMPs, and chemotactic passage, that promote entry of T cells into extravascular tissues.

Key words: adhesion, migration, protease, lymphocyte, immunity, connective tissue

Mononuclear phagocytes, granulocytes, and T cells produce and secrete matrix metalloproteinases (MMPs), with cellular specificity both in the representation of individual MMPs and in the mechanisms of expression of MMP activities [Birkedal-Hansen et al., 1993; Shapiro et al., 1994; Woessner, 1994; Busiek et al., 1995; Corcoran et al., 1995]. Macrophage secretion of MMP-1 and -9 is enhanced by contact with several different connective tissue matrix proteins and suppressed by cytokines such as IL-4 and IL-10 [Corcoran et al., 1992, 1995; Shapiro et al., 1993; Mertz et al., 1994; Busiek et al., 1995]. T cell secretion of MMP-2 and -9 is stimulated by diverse low m.w. mediators, including eicosanoids and neuropeptides, some interleukins and chemokines, and vascular cell adhesion molecule-1 (VCAM-1)–dependent adherence to endothelial cells [Romanic and Madri, 1994; Leppert et al., 1995b; Xia et al., 1996b; Goetzl et al., 1996]. None of the interactions of T cells with connective tissue matrix proteins have been examined in relation to regulation of production, secretion, or activation of the MMPs.

The distinctive effector functions of activated MMPs in immune responses include facilitation of secretion of active tumor necrosis factor by cleavage of the membrane bound form [McGeehan et al., 1994], proteolytic shedding of some cytokine receptors [Crowe et al., 1995], release of active growth factors from binding protein complexes and tissue stores [Fowlkes et al., 1994; Taipale et al., 1995], and mediation of immune cellular migration across basement membranes (BMs) by proteolytic generation of channels required for passage [Leppert et al., 1995a,b; Goetzl et al., 1996; Xia et al., 1996]. Human blood mixed T cells and human cultured T lymphoblastoma cells migrate across a Matrigel

Abbreviations used: FBS, fetal bovine serum; LTB4, leukotriene B4; MESF, molecule of equivalent soluble fluorochromes; MMP, matrix metalloproteinase; P, penicillin; PGE2, prostaglandin E2; S, streptomycin; VCAM, vascular cell adhesion molecule; VIP, vasoactive intestinal peptide.

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model BM through an MMP-dependent process stimulated by prostaglandin E2 (PGE2), leukotriene B4 (LTB4), IL-2, IL-4, and vasoactive intestinal peptide (VIP), and suppressed by specific MMP inhibitors [Leppert et al., 1995a,b; Xia et al., 1996b]. T cell constitutive expression of MMP-9 is augmented and expression of MMP-2 is induced by these same stimuli, as demonstrated by quantification of increases in mRNA, protein antigen, and zymographic activity, as well as MMP-dependent cleavage of ^{3}H-type IV human collagen in the Matrigel membrane of migration chambers [Xia et al., 1996b].

Numerous studies have documented increases in expression and activation of integrins by T cells responding to chemotactic factors, exposed to connective tissue proteins, or interacting with other cells [Dustin and Springer, 1991; Bevilacqua, 1993; Imhof and Dunon, 1995]. Induction of MMPs by many stimuli of nonimmune cells depends on signals from integrins [Grinnell, 1994; Riikonen et al., 1995]. The data presented here are from studies designed to elucidate roles of beta1 integrins in T cell adherence and expression of MMP activity required for migration across a fibronectin-enriched model BM. VIP is selected as a known stimulus of T cell adherence to connective tissue proteins and chemotaxis [Johnston et al., 1994; Xia et al., 1996b], and because the target T cells are human $CD4^+8^+$ T lymphoblastoma cells of the Tsup-1 line and human blood–derived $CD4^+$ T cells, both of which express high levels of VIP receptors [O'Dorisio et al., 1986; Xia et al., 1996b].

METHODS

Tsup-1 Cells and $CD4^+$ T Cells

Tsup-1 cells (American Type Culture Collection) were cultured in RPMI-modified Dulbecco's medium (UCSF Cell Culture Facility) with 10% (v:v) fetal bovine serum (FBS) (Hyclone, Inc., Logan, UT), 100 U/ml of penicillin G (P), and 100 μg/ml of streptomycin (S) at a density of 0.5–1.0 × 10^6/ml, as described [Leppert et al., 1995b; Xia et al., 1996a]. T cells were isolated from sodium citrate–anticoagulated venous blood of normal human subjects by sequential dextran sedimentation of erythrocytes, removal of granulocytes, and residual erythrocytes by centrifugation on cushions of Ficoll-Hypaque (Pharmacia, Piscataway, NJ) and elimination of monocytes and most B cells by adherence to plastic petri dishes and then Sephadex G-10 by column filtration, as described [Goetzl et al., 1984]. To isolate $CD4^+$ T cells, suspensions of 1 × 10^7 T cells in 10 ml of RPMI-3% FBS-P/S were incubated for 90 min at room temperature in 100 mm diameter plastic petri dishes that had been precoated at 4°C overnight with 50 μg of mouse IgG1 kappa monoclonal anti-CD4 (Zymed Laboratories, Inc., So. San Francisco, CA) in 5 ml of Hanks' balanced salt solution. After unbound T cells were removed by aspiration of medium and two 10 ml washes of RPMI, bound $CD4^+$ T cells were recovered by scraping into 10 ml of cold calcium- and magnesium-free Hanks' solution. The purity, as assessed by FACS analysis of an aliquot, was >97% with FITC-anti-CD4 and >96% with FITC-anti-CD3 (Zymed), and showed fewer than 3% suppressor-cytotoxic (CD8) T cells and fewer than 1% monocytes (CD14), B cells (CD19 and CD20), or NK cells (CD16, CD56) (Zymed). As part of two of the studies, the $CD4^+$ blood T cells were subjected to negative selection on anti-CD8-coated dishes, which did not affect any of the results. Tsup-1 cells and purified $CD4^+$ T cells were washed once and resuspended in Iscove's medium with 2% (v:v) Nutridoma (Boehringer Mannheim Corp., Indianapolis, IN) for studies of chemotaxis and MMP activity, and Hanks' solution for adherence assays.

Flow Cytometric Analyses of Integrins

Rat monoclonal IgG anti-beta1 (AIIB2) and anti-alpha5 antibodies (BIIG2), the isotype control BIVF2 [Werb et al., 1989], and mouse monoclonal IgG2b anti-alpha4 (MAB1954, clone P4C2, Chemicon International, Temecula, CA), which had been shown to block integrin-dependent functions, were purified by Sepharose HP-protein G affinity chromatography (Sigma). Rat IgG2b anti-alpha6 (MAB1972, clone CLB-701, Chemicon) was purchased in purified form. Suspensions of 1 × 10^6 Tsup-1 cells in 0.2 ml of Hanks' OA at 4°C were incubated with 5–200 ng of anti-integrin antibody for 60 min, washed three times, and incubated in 0.2 ml of Hanks' OA for 30 min with affinity-purified FITC-rabbit anti-rat IgG or FITC-goat anti-mouse IgG (Zymed Laboratories, So. San Francisco, CA). Flow cytometry was performed with a FACScan (Becton-Dickinson, San Jose, CA), using the LYSIS II software program. Log channel fluorescence intensity was determined for propidium iodide-negative cells and converted to molecules of equivalent soluble fluorochromes (MESF) by comparison with the intensity of

calibrated fluorescent microbead standards (10,000–500,000 MESF mixture; Flow Cytometry Standards, San Juan, PR).

Quantification of Adherence and Chemotaxis

Suspensions of 3×10^6 Tsup-1 or CD4$^+$ cells in 3 ml of protein-free Hanks' solution were incubated for 2 hr at room temperature with 1 μM 5-chloromethylfluorescein diacetate (Molecular Probes, Inc., Eugene, OR). The fluorescently labeled cells were washed three times in 10 ml of RPMI-Nutridoma and twice in Hanks' solution with 0.1 g/100 ml of ovalbumin (OA), and then resuspended in 10 ml of Hanks' OA. Replicate 0.2 ml aliquots of each suspension were preincubated for 20 min at room temperature with anti-integrin antibody and spread evenly on the flat bottoms of 12-well plates that had been coated with 2 μg each of purified human fibronectin (Sigma, St. Louis, MO), and preincubated for 1 hr at room temperature with 0.5 ml of 3 g/100 ml of BSA in Hanks' solution. After 2 hr at 37°C, the plates were rocked for 2 min and nonadherent cells harvested and diluted to 2 ml for assessment of fluorescence intensity in a Perkin-Elmer LS50B spectrometer. Percentage adherence was calculated relative to the total fluorescence of cells added to each well (100%). Spontaneous release of dye in buffer alone was a mean of 12 ± 9% (n = 16), was always less than 27%, and was not altered by anti-integrin antibody or VIP. Adherence determined by counting cells that remained on the bottom of wells was within 8% of the fluorometrically derived value (n = 36). Chemotaxis of Tsup-1 and CD4$^+$ T cells completely through polycarbonate filters coated with 12 μl of Matrigel was quantified as described by microscopic counts in fluid from the lower compartment [Leppert 1995a,b; Xia et al., 1996b], except that 1 μg of human fibronectin was mixed in the Matrigel on each filter. Control chemotactic values for each concentration of VIP (100%) were the mean number of cells that crossed each filter to the lower compartment without antibody pretreatment, after correction for spontaneous migration without a stimulus, and the responses of antibody-pretreated cells were expressed as a percentage of the respective controls.

Determination of T Cell MMP Activity

Zymographic analysis of MMP activity secreted by T cells, which was predominantly MMP-9 and lesser amounts of MMP-2, was performed as described [Leppert et al., 1995a] by electrophoresis in nonreducing SDS 10% polyacrylamide gels copolymerized with 1 mg/ml of type A gelatin. The decrease in Coomassie blue staining of each band of MMP activity was quantified densitometrically (Scan-Jet IIC, Hewlett-Packard, Boise, ID; Image 1.41 software, NIH) and changes are expressed as a percentage of untreated controls. To assess matrix degradation by migrating T cells, 0.3 μg (4.4×10^5 dpm) of ^{3}H type IV human collagen (N-[propionate-2,3-^{3}H]; 1.08 μCi/μg, Dupont New England Nuclear, Boston, MA) was mixed thoroughly with the 12 μl of Matrigel–fibronectin coating each filter. Replicate 50 μl aliquots were removed from the lower compartment of the chambers after 4 hr for quantification of soluble radioactivity by liquid scintillation counting.

RESULTS AND DISCUSSION

The display of integrins by Tsup-1 cells was defined initially by fluorescence flow cytometry, using each purified monoclonal anti-integrin chain antibody at the same IgG concentration. The signal intensity of Tsup-1 cells labeled with FITC-rabbit anti-rat IgG alone was a mean of 20 kMESF and increased to means of 70 kMESF and 29 kMESF, respectively, when incubated first with anti-beta1 and anti-alpha5 antibodies. Signal intensity from labeling with FITC-goat anti-mouse IgG alone was a mean of 14 kMESF and increased to a mean of 43.5 kMESF with anti-alpha4 antibody. In contrast, primary incubation with rat anti-alpha6 antibody did not increase detectably the fluorescence signal of the FITC-rabbit anti-rat IgG. Thus the rank order of abundance of the beta1 integrins represented on Tsup-1 cells is alpha4 > alpha5 ≫ alpha6, which resembles that of blood CD4$^+$ T cells.

The capacity of anti-integrin blocking antibodies to inhibit VIP-enhanced adherence of Tsup-1 cells to fibronectin was examined with a fluorescence assay, after labeling the cells with a noncytotoxic diacetate derivative of fluorescein. The anti-beta1 integrin antibody inhibited adherence most effectively, in a concentration-dependent relationship, such that 1 μg/ml resulted in 70% suppression of the adherence induced by 3×10^{-8} M VIP and 39% of that evoked by 3×10^{-7} M VIP (Fig. 1). At these respective concentrations of VIP, the increment in adherence was eliminated completely by 3 and 10 μg/ml of the anti-beta1 antibody. As expected from the preva-

lence of the alpha chains defined by flow cytometry, antibody to alpha4 was more active than that to alpha5 in inhibiting the increments in adherence evoked by both concentrations of VIP, whereas neither an isotype control for anti-beta1 nor anti-alpha6 antibody had an effect on adherence of Tsup-1 cells (Fig. 1). The integrin dependence of 3×10^{-7} M VIP-enhanced adherence of $CD4^+$ T cells to fibronectin was similar to that of Tsup-1 cells, as mean inhibition (n = 2) by 1, 3, and 10 μg/ml of anti-beta1 antibody was 26, 54, and 90%, respectively; by anti-alpha4 antibody was 20, 46, and 80%; and by anti-alpha5 antibody was 0, 18, and 46%, but there was no detectable effect of anti-alpha6 antibody.

Secretion of MMP-9, and lesser amounts of MMP-2, by Tsup-1 cells is enhanced by VIP, with maximal mean increases of threefold after 4 hr of stimulation by 10^{-7} M VIP, as assessed by zymography and Western blots [Leppert et al., 1995b; Xia et al., 1996b]. Preincubation of suspensions of Tsup-1 cells and $CD4^+$ T cells with 10 μg/ml of each of the anti-integrin neutralizing antibodies prior to introduction of 3×10^{-7} M VIP had no significant effect on secretion of MMPs. The secretions of MMP-9 zymographic activity by Tsup-1 cells pretreated with antibodies to beta1, alpha4, and alpha5 chains and then incubated for 4 hr with 10^{-7} M VIP were, respectively, means of 0.9-, 1.0-, and 0.8-fold that of the Tsup-1 cells incubated with VIP alone, which was 2.2-fold higher than that of buffer controls. Similar anti-beta1, alpha4, and alpha5 integrin antibody treatment and VIP exposure of $CD4^+$ T cells resulted in secretions of MMP-9 zymographic activity that were, respectively, means of 1.0-, 1.1-, and 1.2-fold that of the $CD4^+$ T cells incubated with VIP alone, which was 4.1-fold higher than that of buffer controls.

In contrast to the lack of effect of anti-integrin antibodies on VIP-stimulated secretion of MMP activity by T cells in suspension, the MMP-dependent degradation of type IV collagen by T cells migrating through fibronectin–Matrigel in response to the higher concentration of VIP was suppressed significantly in antibody concentration-dependent relationships (Fig. 2). The dependence of type IV collagen cleavage on MMP activity of migrating Tsup-1 cells was confirmed by the greater than 80% mean suppression attained by the specific MMP inhibitor GM6001 (Glycomed, Alameda, CA) [Leppert et al., 1995a,b]. At the same concentrations, anti-beta1 IgG was more inhibitory than anti-alpha4 IgG, and neither anti-alpha6 IgG nor an isotype

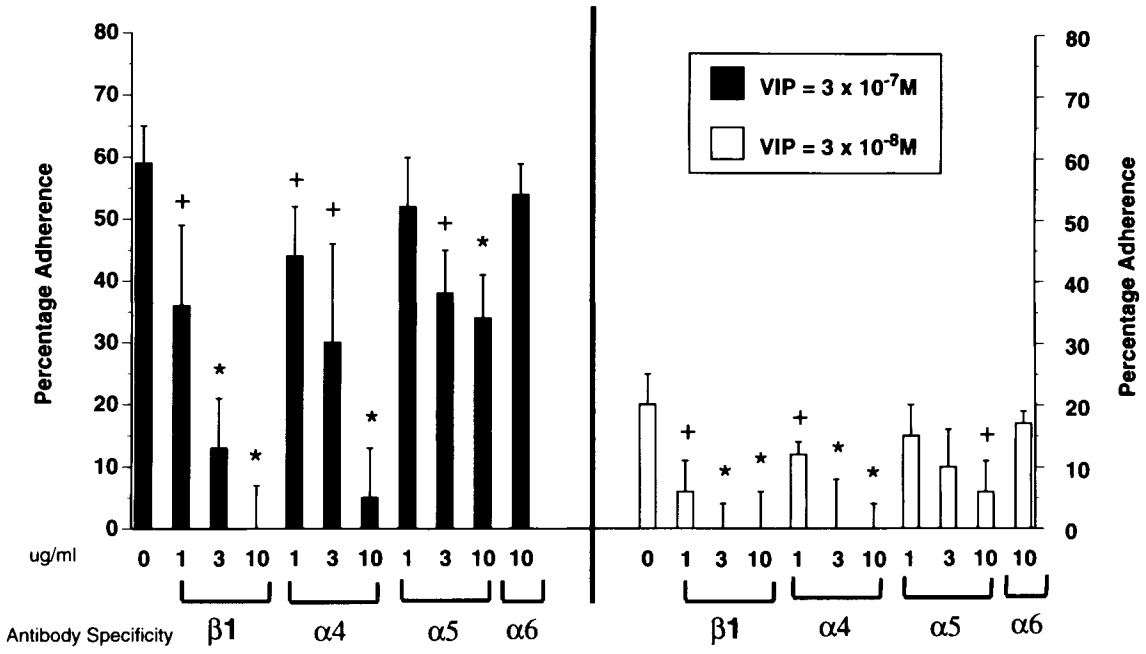

Fig. 1. Suppression of Tsup-1 cell adherence to fibronectin by anti-integrin monoclonal antibodies. Each bar and bracket represents the mean ± SD of the results of three different studies performed in duplicate. The level of significance of suppression of adherence by each concentration of antibody relative to control adherence with buffer alone was calculated by a paired Student's *t* test and depicted by the symbols † = $P < 0.05$ and * = $P < 0.01$.

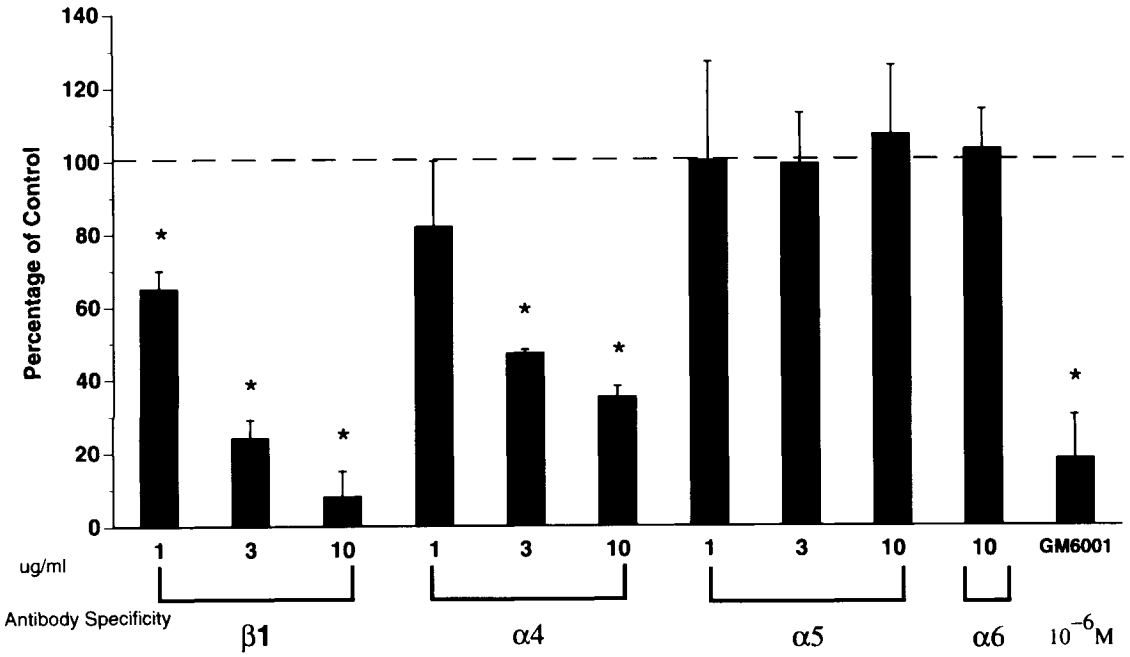

Fig. 2. Suppression of Tsup-1 cell degradation of ^{3}H type IV collagen in Matrigel by anti-integrin monoclonal antibodies. The derivation of each bar and bracket and the meaning of the statistical symbols are as in Figure 1. The mean level of degradation of type IV collagen (±SD) by unstimulated control cells was 1,227 ± 282 dpm, and by Tsup-1 cells stimulated with 3×10^{-7} M VIP was 3,921 ± 295 (100%).

control for anti-beta1 had an effect, as was the case for suppression of VIP-enhanced adherence. Anti-alpha5 IgG, which inhibited VIP-enhanced adherence of Tsup-1 cells to fibronectin least significantly (Fig. 1), had no detectable effect on the degradation of type IV collagen by Tsup-1 cells responding to the higher concentration of VIP (Fig. 2).

Degradation of type IV collagen in Matrigel by $CD4^+$ T cells migrating to 3×10^{-7} M VIP also was highly dependent on MMP activity, as evidenced by mean inhibition of 91% by 10^{-6} M GM6001. Inhibition of $CD4^+$ T cell degradation of type IV collagen in Matrigel by 10 μg/ml of antibodies to the beta1, alpha4, alpha5, and alpha6 chains paralleled that observed for Tsup-1 cells with mean levels of 98%, 74%, 5%, and 7%, respectively. Significant suppression of MMP-dependent degradation of type IV collagen by concentrations of anti-integrin antibodies that had no effect on secretion of MMPs by T cells in suspension may reflect requirements for substrate adherence sufficient to allow direct delivery of high concentrations of MMP and to permit migration to undigested substrate. The former possibility is speculative, but the latter is supported by the concomitantly lower level of inhibition by anti-alpha5 antibody of VIP-stimulated chemotaxis of T cells through fibronectin–Matrigel (Fig. 3).

The roles of integrin-dependent adherence to fibronectin and degradation of fibronectin–Matrigel in the chemotactic responses of T cells to VIP were evaluated by pretreatment with the same panel of monoclonal antibodies (Fig. 3). Antibody concentration-dependence relationships similar to those for inhibition of VIP-enhanced adherence and MMP effects were observed for suppression of VIP-evoked chemotaxis of Tsup-1 cells by anti-beta1 and anti-alpha4 antibodies. Anti-alpha6 antibody and the isotype control for anti-beta1 had no effect on chemotaxis. The anti-alpha5 antibody had no effect on chemotaxis elicited by the higher concentration of VIP and only a moderate suppressive effect on chemotaxis to the lower concentration of VIP, compared to the anti-beta1 and anti-alpha4 antibodies. The same levels of 1, 3, and 10 μg/ml of the monoclonal antibodies suppressed chemotaxis of $CD4^+$ T cells evoked by the lower concentration of VIP to means (n = 2) of 24, 8, and 0% of control, respectively, with anti-beta1 antibody; 31, 26, and 2% with anti-alpha4 antibody; and 44, 31, and 19% with anti-alpha5 antibody. Corresponding values for suppression of $CD4^+$ T cell chemotaxis to the higher

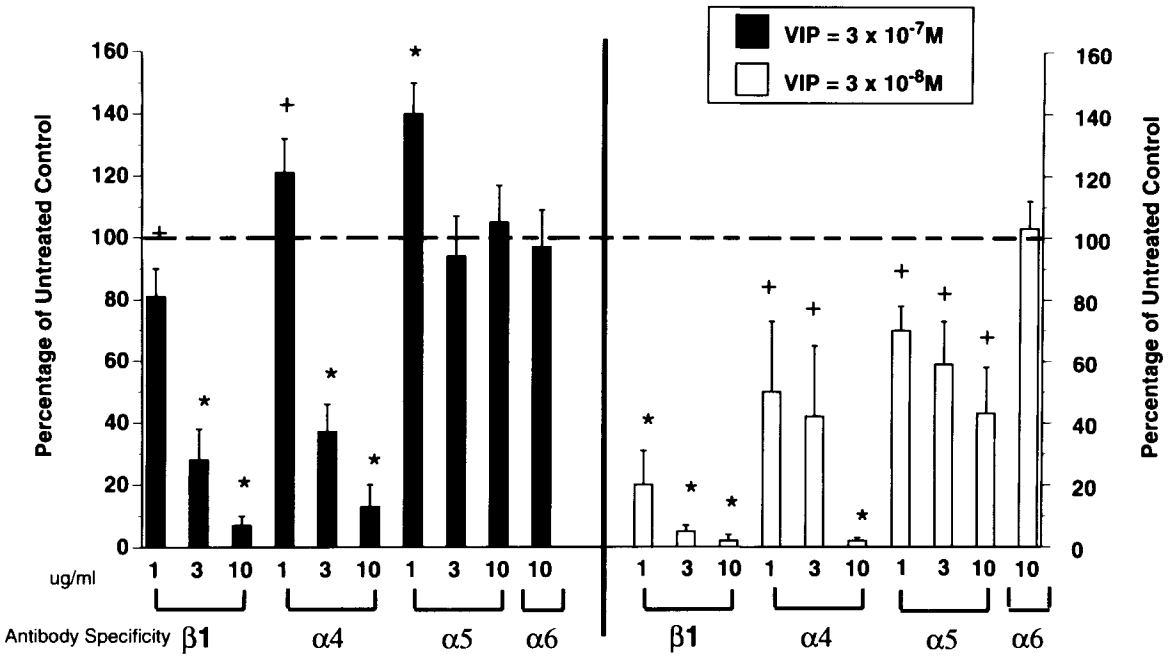

Fig. 3. Effects of anti-integrin monoclonal antibodies on Tsup-1 chemotaxis through fibronectin–Matrigel. The derivation of each bar and bracket and the meaning of the statistical symbols are as in Figure 1. At a concentration of 3×10^{-8} M, VIP stimulated trans-Matrigel chemotaxis by a mean ±SD of 11 ± 3.3% of the total number of Tsup-1 cells added to the chambers, as compared to 4.8 ± 1.4% in the absence of a stimulus. At a concentration of 3×10^{-7} M, VIP stimulated chemotaxis by 18 ± 4.5% of the total initial Tsup-1 cells, as compared to 6.3 ± 4.9% without a stimulus.

concentration of VIP were 68, 19, and 2% of control, respectively, with anti-beta1 antibody; −16 (enhancement as for Tsup-1 cell chemotaxis), 47, and 10% with anti-alpha4 antibody; and −31, 105, and 96% with anti-alpha5 antibody.

For the higher concentration of VIP, the lack of suppression of T cell chemotaxis by alpha5 neutralization resembles the absence of effect on MMP activity (Fig. 2). In contrast, enhancement of adherence of T cells by the high concentration of VIP was inhibited by anti-alpha5 antibody, but only modestly by up to 40% compared to over 95% by either anti-beta1 or anti-alpha4 antibodies (Fig. 1). Thus the modest degree of inhibition of VIP-enhanced adherence of T cells to fibronectin, achieved by neutralizing the less abundant alpha5 chain, was insufficient to suppress VIP stimulation of either expression of MMP activity by the T cells or their trans-fibronectin-Matrigel chemotactic response. In contrast, the parallel dependence of MMP activity and chemotaxis evoked by the higher concentration of VIP on the more abundant alpha4/beta1 integrin was demonstrated by the similar extent of suppression of both by anti-alpha4 and anti-beta1 antibodies (Figs. 2, 3). That chemotaxis of Tsup-1 cells and $CD4^+$ T cells elicited by the higher concentration of VIP was stimulated significantly by the lowest level of both anti-alpha4 and anti-alpha5 antibodies suggested that the maximal effect of VIP had enhanced expression of the beta1 integrins beyond that required for optimal chemotaxis to a level that included a brake which slightly retarded chemotaxis. Neutralization of this excess integrin by a low concentration of antibody to either alpha4 or alpha5 chain increased the chemotactic response, whereas even the lowest concentration of the more potent antibody reactive with all beta1 integrins suppressed part of the adherence required for an optimal response as well as the excess and thereby inhibited chemotaxis (Fig. 3).

T cells thus appear to respond as do other cells to contact with extracellular matrix proteins by enhanced activity of MMPs [Grinnell, 1994; Riikonen et al., 1995]. The beta1 integrins transduce the signal of matrix protein contact to increased generation of MMPs in many cells, and the surface density of each beta1 integrin determines the magnitude of its contribution to the integrated MMP response. The amounts of

MMPs contained and generated by T cells are smaller than those of macrophages and other phagocytes. Therefore, the consequence of integrin-mediated responses of T cell MMPs to contact with matrix proteins is manifested most clearly in effects such as the passage of T cells through connective tissue, rather than by bulk degradation of connective tissue matrix or effects on other cells. The maximal extent of degradation of type IV collagen by the migrating T cells was 1% (Fig. 2), but a high level of dependence on MMP activity was observed for T cell trans-BM chemotaxis (Fig. 3), which supports the critical role of endogenous MMP activity in T cell function.

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