Differential Regulation of CXCR4-mediated T-cell Chemotaxis and Mitogen-activated Protein Kinase Activation by the Membrane Tyrosine Phosphatase, CD45*

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The chemokine receptor CXCR4 and its cognate ligand, stromal cell-derived factor-1α (CXCL12), regulate lymphocyte trafficking and play an important role in host immune surveillance. However, the molecular mechanisms involved in CXCL12-induced and CXCR4-mediated chemotaxis of T-lymphocytes are not completely elucidated. In the present study, we examined the role of the membrane tyrosine phosphatase CD45, which regulates antigen receptor signaling in CXCR4-mediated chemotaxis and mitogen-activated protein kinase (MAPK) activation in T-cells. We observed a significant reduction in CXCL12-induced chemotaxis in the CD45-negative Jurkat cell line (J45.01) as compared with the CD45-positive control (JE6.1) cells. Expression of a chimeric protein containing the intracellular phosphatase domain of CD45 was able to partially restore CXCL12-induced chemotaxis in the J45.01 cells. However, reconstitution of CD45 into the J45.01 cells restored the CXCL12-induced chemotaxis to about 90%. CD45 had no significant effect on CXCR4 or human immunodeficiency virus gp120-induced internalization of the CXCR4 receptor. Furthermore, J45.01 cells showed a slight enhancement in CXCL12-induced MAP kinase activity as compared with the JE6.1 cells. We also observed that CXCL12 treatment enhanced the tyrosine phosphorylation of CD45 and induced its association with the CXCR4 receptor. Pretreatment of T-cells with the lipid raft inhibitor, methyl-β-cyclodextrin, blocked the association between CXCR4 and CD45 and markedly abolished CXCL12-induced chemotaxis. Comparisons of signaling pathways induced by CXCL12 in JE6.1 and J45.01 cells revealed that CD45 might moderately regulate the tyrosine phosphorylation of the focal adhesion components of the related adhesion focal tyrosine kinase/Pyk2, focal adhesion kinase, p130Cas, and paxillin. CD45 has also been shown to regulate CXCR4-mediated activation and phosphorylation of T-cell receptor downstream effectors Lck, Zap-70, and SLP-76. Our results show that CD45 differentially regulates CXCR4-mediated chemotactic activity and MAPK activation by modulating the activities of focal adhesion components and the downstream effectors of the T-cell receptor.

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The chemokine CXCL12 and its corresponding receptor CXCR4 play an important role in immune and inflammatory responses, lymphopoiesis in bone marrow, and in embryonic developmental processes (1–7). Targeted disruption of either CXCR4 or CXCL12 protein leads to severe defects that are embryologically lethal (3–6). CXCR4 has also been shown to act as a coreceptor for the T-cell tropic human immunodeficiency virus (HIV),† type 1 strain and to play a crucial role in HIV pathogenesis (8–10).

Although CXCL12 acts as a potent chemoattractant for various cell types including T-cells and regulates the directional movement of these cells, relatively little is known about the signaling pathways that may mediate these effects (1, 11). We and others (12–16) have recently deciphered the molecular mechanisms involved in regulating CXCR4 and CCR5-mediated chemotaxis. We have demonstrated that CXCL12 binding to CXCR4 stimulates multiple signaling pathways including activation of focal adhesion components such as the related adhesion focal tyrosine kinase (RAFTK, also known as Pyk2 or Csk-β), focal adhesion kinase (FAK), paxillin, and p130Cas (12). Furthermore, protein-tyrosine phosphatases SHP1 and SHP2 have also been shown to be involved in CXCR4- or CCR5-mediated chemotaxis (13, 15, 17). Hematopoietic cells derived from mice lacking SHP1 showed altered patterns of chemotactic response to CXCL12 (17). SHP2 was shown to associate with CXCR4 and to regulate the CXCL12-induced migration of T- and pre-B-cells (15). In the present investigation, we further delineated the role of tyrosine phosphatases and showed that the membrane-bound tyrosine phosphatase CD45 is a key regulator of CXCL12-induced and CXCR4-mediated chemotaxis.

CD45 is expressed exclusively on cells of hematopoietic lineage (18–20). It is a key regulator of antigen receptor signaling in T- and B-cells, playing a pivotal role in the activation and development of lymphocytes (18–23). Studies using CD45-deficient mice and cell lines revealed that this phosphatase is very important for thymocyte differentiation (24, 25). CD45 is shown to influence the early events in T-cell activation by operating as a positive, as well as negative, regulator of the Src family kinases, p56Lck and p59Fyn. Recent studies have also identified CD45 as a negative regulator of cytokine-mediated signaling by acting as a JAK tyrosine phosphatase (26). Thus, CD45 plays a crucial role in cytokine receptor-mediated differentiation, proliferation, and anti-viral responses. In addition, CD45 is also required for some integrin-mediated adhesion...
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Although our understanding of the molecular mechanisms of CD45 in regulating TCR and cytokine receptor signaling have increased substantially, its role in chemokine-mediated biological functions has not been explored. In the present study, we have investigated the role of CD45 in regulating CXCL12-induced chemotaxis and MAP kinase activation in T-cells. Our data indicate a prominent role for CD45 in these processes and thus provide new information regarding CXCR4-mediated chemotactic signaling pathways.

EXPERIMENTAL PROCEDURES

Reagents and Materials—Purified antibodies to phospo-specific p44/42 MAP kinase were obtained from New England Biolabs (Beverly, MA). Antibodies to p44/42 protein, phosphotyrosine (pTyr), and p56Lck were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Phosphospecific antibodies to RAFTK (Pyk2, pTyr402), p44/42 MAP kinase were obtained from New England Biolabs (Beverly, MA). Antibodies to p44/42 protein, phosphotyrosine (pTyr 99), and p44/42 MAP kinase were obtained from New England Biolabs (Beverly, MA).

RESULTS

Chemotaxis Assays—Chemotaxis assays were performed in 24-well plates containing 5-μm porous inserts (Costar Corporation, Kennebunk, ME). 100 μl (1 x 10^6 cells) from each cell line (J45.01, JE6.1, J45/CH11, J45/A2, J45/LB3) was loaded onto the upper well. 0.6 ml of medium containing CXCL12 (0, 10, 50, 100 ng/ml) was added onto the lower well. The plates were incubated for 3 h at 37°C in 5% CO_2. After incubation, the inserts were removed carefully, and the viable cells were counted using standard procedures. The results are expressed as the number of cells migrating to the bottom chamber. Each experiment was performed three or four times in triplicate.

Kinase Assay—Kinase assay of the Src family member, Lck, was done as described (32). Briefly, the immune complexes obtained by immunoprecipitation of the cell lysates with antibodies to Lck were washed twice with radioimmunoprecipitation assay buffer and then washed with kinase buffer (20 mM HEPES, pH 7.4, 50 mM NaCl, 10 μM Na_2VO_3, 5 mM MgCl_2, 5 mM MnCl_2). Finally, the immune complexes were incubated in a total volume of 25 μl of kinase buffer containing enolase 15 μg, 0.01% BSA, MgCl_2, MnCl_2, and 1 μCi [γ-32P]ATP for 30 min at 30°C. The proteins were separated on 12% SDS-PAGE. Bands were detected by autoradiography.

Flow Cytometry—The CXCR4 or CD45 receptor on the JE6.1, J45.01, J45/CH11, J45/A2, or J45/LB3 cells was stained with anti-CXCR4 or anti-CD45 antibodies overnight at 4°C, followed by staining with secondary antibody coupled to Texas red or fluorescein isothiocyanate (Vector Laboratories) or phosphatidylserine (Amerham Biosciences). The cells were cytospun on slides, and the expression of these proteins was visualized using a Leica TCS confocal microscope.

Confocal Microscopy—Confocal microscopy studies were done as described earlier (33). Briefly, Jurkat (JE6.1 clones) were washed twice with Hank’s-buffered salt solution (Celgro) and resuspended in Hank’s-buffered salt solution at a density of 10^7 cells/ml for 1 h at 37°C. Serum-starved cells were stimulated with 100 ng/ml CXCL12 at 37°C for various time periods. Following stimulation, the cells were washed with ice-cold phosphate-buffered saline and fixed in 4% paraformaldehyde for 10 min at room temperature. The next, the cells were permeabilized with 0.1% Triton X-100 and 0.1% sodium citrate for 2 min on ice. The cells were washed once with 1x PBS and blocked with 5% bovine serum albumin for 20 min at room temperature. The cells were stained with anti-CXCR4 antibody as discussed above and then washed with PBS, suspended in 1% formaldehyde in PBS, and then washed with PBS. The cells were cytospun on slides, and the expression of these proteins was visualized using a Leica TCS confocal microscope.

Flow Cytometry—The CXCR4 or CD45 receptor on the JE6.1, J45.01, J45/CH11, J45/A2, or J45/LB3 cells was stained with phycocerythrin (PE)-coupled anti-CXCR4 or CD4 antibodies for 1 h at 4°C. For CXCR4 down-modulation analysis, JE6.1 or J45.01 cells were stimulated with CXCL12 (1 μg/ml) or HIV gp120 (1.2 μg/ml) for various time periods (0, 2, 4, 6 h). Following stimulation, the cells were washed with ice-cold PBS and then washed with 2% formaldehyde for 15 min at room temperature. The cells were stained with anti-CXCR4 antibody as discussed above and then washed with PBS, suspended in 1% formaldehyde in PBS, and subjected to flow cytometric analysis.

Statistical Analysis—Statistical analysis of data obtained from three or four experiments performed in duplicate or triplicate. The statistical significance was determined by the Student’s t test.

RESULTS

CXCL12-induced and CXCR4-mediated Chemotaxis Is Reduced in CD45-deficient Cells—CXCL12-induced chemotaxis has been shown to be regulated by tyrosine phosphatases SHP1 and SHP2 (15, 17). We have further extended these studies to evaluate the role of CD45 in CXCL12-mediated and CXCL12-
induced chemotaxis. To examine the involvement of CD45 in the regulation of CXCL12-induced chemotaxis, the CD45-deficient Jurkat cell line J45.01 and CD45-expressing JE6.1 cells were assessed for their ability to migrate in response to different concentrations of CXCL12. The CD45-deficient J45.01 cells showed a reduced response (~75%) toward CXCL12-induced (50 ng/ml) chemotaxis in comparison to the control JE6.1 Jurkat cells (Fig. 1A).

The difference in chemotactic response toward CXCL12 was consistent over a concentration range of 10–100 ng/ml, levels at which optimal migration has been reported (16). However, migratory response was less significant at higher concentrations of CXCL12 (500–1000 ng/ml) (data not shown). Next, we identified the region of CD45 important for CXCL12-induced chemotaxis by assaying the ability of transfectants expressing hybrid CD45 cDNA to restore chemotaxis. As shown in Fig. 1, B and D, CD45-deficient Jurkat cells expressing a chimeric protein consisting of the extracellular domain and transmembrane region of the class I major histocompatibility complex protein and the cytoplasmic domain of CD45 (J45/CH11) partially restored the CXCL12-induced chemotaxis as compared with cells expressing only the extracellular and transmembrane regions of the class I major histocompatibility complex protein (J45/A2). Furthermore, reconstitution of J45.01 cells with normal human CD45 (J45/LB3) significantly restored the CXCL12-induced chemotaxis (Fig. 1C). These results show that expression of the full-length CD45 (J45/LB3) restored the chemotaxis to about 90%, whereas cells expressing only the cytoplasmic domain of CD45 (J45/CH11) restored the chemotaxis to about 65% as compared with the JE6.1 parental cell line (Fig. 1D). Similar levels of CXCR4 receptor were expressed by all cell lines (data not shown).

Therefore, the differences in chemotaxis observed in the various Jurkat clones and transfectants are not because of variation in CXCR4 levels.

CD45 Does Not Regulate CXCR4 Internalization—CXCL12 and gp120 at higher concentrations have been shown to induce CXCR4 receptor internalization (33). CXCR4 trafficking is important in HIV infection and immune regulation. Recently, we have shown that the proteasome pathway regulates CXCL12-induced down-modulation and chemotaxis (33). In Fig. 1, we have shown that CD45 regulates CXCL12-induced chemotaxis. Thus, we next explored the role of CD45 in the ligand-induced down-modulation of the CXCR4 receptor. No significant difference in CXCL12 or HIV gp120-induced down-modulation of CXCR4 was observed between the CD45-positive JE6.1 (Fig. 2A) and CD45-negative J45.01 (Fig. 2B) cells. These results suggest that CD45 does not regulate the CXCL12- or gp120-induced pathway leading to CXCR4 internalization.

CXCL12-induced Tyrosine Phosphorylation of CD45 and Its Association with the CXCR4 Receptor—To investigate further CD45-regulated chemotactic signaling mechanisms, we first determined the tyrosine phosphorylation status of CD45 upon CXCL12 treatment in the CD45-positive JE6.1 cells. As shown in Fig. 3A, CXCL12 stimulation induced the increased tyrosine phosphorylation of CD45. This phosphorylation was rapid and reached a maximum level between 0.5 to 2.5 min. Equal amounts of CD45 protein were present in each lane (Fig. 3A, bottom panel). We also investigated whether the CXCR4 recep-
Fig. 3. Tyrosine phosphorylation of CD45 and its association with CXCR4 upon stimulation with CXCL12. CD45-positive variant (JE6.1) cells (A and B) or peripheral blood lymphocytes (C) were either unstimulated (0) or stimulated with CXCL12 (100 ng/ml) for the indicated time periods. Cells were lysed and immunoprecipitated (IP) with CD45 (A) or CXCR4 (B and C) antibody. The immune complexes were separated on 7% SDS-PAGE gel, transferred to nitrocellulose membrane, and immunoblotted with anti-phosphotyrosine antibody (4G10, pTyr398) (A, top panel) followed by anti-CD45 antibody (A, bottom panel). B and C, the blots were probed with anti-CD45 antibody. Protein loading was analyzed by running 50 μg of lysates on SDS-PAGE and immunoblotting with anti-actin antibody (bottom panels). D, the CD45-positive Jurkat cell clone (JE6.1) was stimulated with CXCL12 (100 ng/ml) for the indicated time point. The cells were fixed with paraformaldehyde and subjected to confocal microscopic analysis using anti-CD45 (green) and anti-CXCR4 (red) antibodies, as described under "Experimental Procedures." Yellow represents the colocalization of CD45 and CXCR4. P-Tyrosine, phosphorylated Tyr; WB, Western blot; TCL, total cell lysates; PBL, peripheral blood lymphocyte; UN, unstimulated.

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CD45 Regulates CXCR4-induced Src-related Kinases—Src kinases have been shown to play an important role in cell migration and adhesion (39, 40). p56 Lck, a member of the Src family of protein-tyrosine kinases, is a physiological substrate of CD45 (18–20). It has been shown that CD45-mediated dephosphorylation of Tyr(505) (Lck) activates this kinase. Therefore, we compared the CXCL12-induced tyrosine phosphorylation and kinase activity of Lck in CD45-positive and -negative cell lines. As shown, CXCL12 increased the kinase activity of Lck (Fig. 5) as compared with the untreated cells in the CD45-positive cell line. However, no significant change in Lck kinase activity was observed in the CXCL12-stimulated CD45-negative cells. We also observed that Lck protein was hyperphosphorylated at tyrosine residues in the CD45-negative cells as compared with the CD45-positive cells. Equal amounts of Lck were present in the cell lysates.

CXCR4-mediated Tyrosine Phosphorylation of Focal Adhesion Components Is Regulated by CD45—Several components of focal adhesion complexes are known to regulate chemokine-mediated chemotaxis (41, 42). These include RAFTK/Pyk2, FAK, paxillin, and p130Cas. These proteins have also been...
shown to be involved in integrin-triggered cell adhesion and cell spreading. Therefore, we examined the importance of CD45 in regulating the tyrosine phosphorylation of these molecules upon stimulation with CXCL12 by using phosphorylation site-specific antibodies. As shown in Fig. 6A, the CXCL12-induced tyrosine phosphorylation of RAFTK at tyrosine residues 402 and 881 was slightly reduced in the CD45-negative cells (J45.01) as compared with the CD45-positive cells (JE6.1). Equal amounts of RAFTK were present in each sample. Similarly, the tyrosine phosphorylation of FAK was slightly reduced at tyrosine residue 397 in the CD45-negative cells as compared with the CD45-positive cells (Fig. 6B). Furthermore, we found that tyrosine phosphorylation of other focal adhesion components, paxillin (Fig. 6C) and p130Cas (Fig. 6D), was also reduced in the CD45-negative cells as compared with the CD45-positive cells.

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FIG. 4. Lipid raft inhibitor disrupts the interaction between CD45 and CXCR4 and blocks CXCL12-induced chemotaxis. A, JE6.1 cells, untreated or pretreated with MBC (10 mM) for 1 h, were stimulated with CXCL12 (100 ng/ml) for the indicated time periods. The cells were lysed, and the lysates were subjected to immunoprecipitation (IP) with anti-CXCR4 antibody. The immunoprecipitates were separated on 7% SDS-PAGE followed by immunoblot analysis with anti-CD45 antibody. Protein loading was analyzed by running 50 μg of lysates on SDS-PAGE and immunoblotting with anti-actin antibody (bottom panel). B and C, JE6.1 cells were preincubated with MBC at different concentrations (mM) in the absence (B) or presence (C) of 2.5% serum. The chemotactic activity of the pretreated cells toward CXCL12 (100 ng/ml) was monitored as described under “Experimental Procedures”; p < 0.005. TCL, total cell lysates; WB, Western blot.

FIG. 5. CD45 modulates CXCL12-induced Lck kinase activity. Lysates obtained from unstimulated (0) or CXCL12-stimulated (100 ng/ml) CD45-negative and -positive cells were immunoprecipitated with anti-Lck antibodies. The immune complex was subjected to an in vitro kinase assay, as described under “Experimental Procedures” (upper panel) by using enolase (acid-denatured) as a substrate. The immune complex was also separated on SDS-PAGE and immunoblotted with anti-phosphotyrosine antibody (4G10) (middle panel). The same blot was stripped and reprobed with anti-Lck antibody (bottom panel). C, antibody control; P-Tyrosine, phosphotyrosine.
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DISCUSSION

This study indicates the central role of the membrane-bound tyrosine phosphatase, CD45, in CXCL12-induced and CXCR4-mediated chemotactic signaling, which plays a critical role in the immune system by regulating the trafficking and positioning of lymphocytes (11–17, 45). CXCR4 and its cognate ligand, CXCL12, have also been shown to play an important role in HIV gene product nef-mediated chemotaxis and breast cancer metastasis (46, 47). However, CXCR4-mediated chemotactic mechanisms are complex and have not been completely defined. We and others (12–17, 44, 45) have shown that CXCR4-mediated chemotaxis involves activation of multiple signaling molecules including tyrosine phosphatases SHP1 and SHP2, focal adhesion components, Src-related kinases, and the T-cell activating molecule ZAP-70. In the present study, we have shown that another important component of the T-cell receptor signaling complex, the membrane-bound tyrosine phosphatase, CD45, also regulates CXCL12-induced and CXCR4-mediated chemotaxis. We observed reduced migration of CD45-negative T-lymphocytes in response to optimal concentrations of CXCL12 (10–100 ng/ml). However, migratory response was less significant at higher concentrations of CXCL12 (500–1000 ng/ml) (data not shown). The effects observed at higher CXCL12 concentrations were similar to those observed by other investigators (48). Reconstitution of full-length CD45 into J45.01 cells almost completely restored the chemotactic response induced by CXCL12. Furthermore, transfection of the cytoplasmic domain of CD45 (containing tyrosine phosphatase activity) into CD45-negative cells was also able to moderately restore the migratory response, suggesting that CD45 phosphatase activity is important for mediating CXCL12-induced chemotactic signaling. The cytoplasmic domain of CD45 has also been shown to be required for TCR-mediated signaling events (22, 23).

The role of CD45 in cell spreading and chemotaxis is controversial. One report (49) indicates that in T-cells, the presence of CD45 prevents cell spreading in response to the binding of CD44, a cell adhesion molecule. However, other studies (27, 50) indicate that CD45 positively regulates integrin-mediated adhesion and spreading in macrophages and the chemotaxis of neutrophils.

Our data show that CXCL12 treatment increases the tyrosine phosphorylation of CD45. Similarly, T-cell activation has been shown to result in the phosphorylation of CD45 on tyrosine and serine residues located in its cytoplasmic domain (51, 52). Phosphorylation of CD45 might regulate its functions by altering its phosphatase activity or by providing docking sites for its interaction with other proteins (52). In the present studies, we observed by immunoprecipitation that CXCL12 treatment induced the association of CD45 with CXCR4. This result was further confirmed by confocal microscopy, which showed that the CXCR4 receptor colocalized with CD45. CD45 has been shown to interact with other cell surface molecules such as CD2, CD4, and TCR (53). We obtained a somewhat
diminished response to CXCL12 in cells transfected with a chimeric molecule containing the cytoplasmic domain of CD45 and the transmembrane and extracellular domains of the HLA-A2 molecule as compared with cells transfected with full-length CD45. Thus, the extracellular and transmembrane domains of CD45 may regulate the magnitude of the CXCL12-induced chemotactic response through efficient coupling of CXCR4 with its signaling complex via CD45.

We have also shown that CD45 interaction with CXCR4 can be inhibited by pretreatment of cells with the lipid raft inhibitor, MBC. Furthermore, MBC was also shown to abrogate CXCR4-mediated chemotaxis in medium deprived of serum. Recently, MBC was shown to inhibit CXCL12-induced chemotaxis and T-cell polarization in cholesterol-depleted cells (38). These results suggest that lipid rafts play an important role in CXCL12-induced chemotaxis. Co-localization of CD45 to lipid rafts in T-cell receptor signaling is still not clear. It has been observed that CD45 is excluded from the lipid raft domain upon TCR signaling (54). However, cross-linking of the CD26 receptor induced an interaction between CD26 and the cytoplasmic domain of CD45 that resulted in the co-aggregation of CD45 and CD26 in lipid rafts (55). The role of CD45 in CXCR4-mediated lipid raft formation is a subject for further studies.

CD45 has been shown to regulate the activity of the Src-related kinase, Lck (18–20). Moreover, Src kinases have been shown to be involved in the CXCL12-induced signaling that regulates chemotaxis (15, 56). Therefore, one possible explanation for the CXCL12-induced inhibition of T-cell migration in CD45-negative cells is the effect of CD45 on Lck. The Lck kinase was hyperphosphorylated at tyrosine residues and possessed reduced kinase activity in the CD45-negative cells. The above data suggest that CXCL12 may stimulate Lck kinase by activating CD45, which, in turn, mediates the dephosphorylation of this kinase at its negative regulatory carboxyl-terminal sites.

In addition to the Src-related kinases, CD45 was also shown to modulate the phosphorylation of focal adhesion components such as RAFTK, FAK, paxillin, and p130Cas. These proteins form signaling complexes that are involved in chemotaxis (41, 42). Our data indicate that CD45 may partially regulate the tyrosine phosphorylation of RAFTK at residues 402 and 881, whereas it regulates FAK phosphorylation at residue 397. These data indicate that CD45 differentially regulates the phosphorylations of RAFTK and FAK at various tyrosine motifs. However, tyrosine residues that bind to Src-related kinases, specifically these pathways modulate T-cell chemotaxis through the regulation of various shared signaling substrates such as CD45, Lck, RAFTK, and FAK. Thus, the molecular mechanisms that regulate T-cell activation and migration may involve common signaling molecules, and hence the coordinated integration of both pathways is likely to play an important role in immune regulation and inflammation.

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