CHROMOSOMAL LOCATION OF THE GENES ENCODING
THE LEUKOCYTE ADHESION RECEPTORS LFA-1, Mac-1
AND p150,95

Identification of a Gene Cluster Involved in Cell Adhesion

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LFA-1, Mac-1 (CR3), and p150,95 are cell surface glycoproteins involved in
leukocyte adhesive interactions (1, 2). The three glycoproteins are α/β hetero-
dimers composed of a common β subunit (M, 95,000; CD18) noncovalently
associated with distinct α subunits of M, 180,000 (LFA-1α; CD11a), 170,000
(Mac-1α; CD11b), or 150,000 (p150,95α; CD11c). LFA-1 is expressed on all
leukocytes and functions in killer T lymphocyte adhesion to target cells, helper
T lymphocyte responses, natural killing, antibody-dependent killing, and in lym-
phocyte and monocyte adhesion to endothelial cells, fibroblasts, and epidermal
keratinocytes. Mac-1 and p150,95 are expressed on monocytes and neutrophils
and on certain activated lymphocytes, and have a dual function as adhesion mol-
ecules in cell–cell and cell–substrate interactions and as complement receptors
for iC3b. LFA-1, Mac-1, and p150,95 are deficient in leukocyte adhesion defi-
cency (LAD),1 an inherited disease caused by mutations in the common β sub-
unit (3, 4).

Recently the cloning and complete amino acid sequences of the LFA-1, Mac-
1 and p150,95 α subunits and the common β subunit have been reported (5–7;
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preparation; Larson, R. S., A. L. Corbi, L. Berman, and T. A. Springer, manu-
script in preparation). The LFA-1, Mac-1 and p150,95 α subunits are transmem-
brane polypeptides with long extracellular domains containing putative divalent
cation-binding sequences (5; Corbi, A. L., et al., Larson, et al., manuscripts in
preparation). The α subunits of LFA-1, Mac-1, and p150,95 are structurally
related: Mac-1α and p150,95α are 63% identical at the amino acid level, while
LFA-1α is 35% identical to Mac-1α and p150,95 α, suggesting a common evo-
lutionary origin for the three polypeptides. The common β subunit is an integral
membrane polypeptide, whose extracellular portion contains four cysteine-rich
homologous repeats (6, 7). Homologies to the extracellular matrix (ECM) recep-
tors define a gene superfamily of α/β complexes termed the integrins involved in both cell–cell and cell–matrix adhesion (5–14).

A number of genes coding for structurally related molecules are organized in clusters. We have tested whether the leukocyte adhesion receptor α subunits are closely genetically linked. The gene for the α subunit of human LFA-1 and the common β subunit have previously been mapped to chromosomes 16 and 21, respectively, by means of somatic cell hybrids (15). We demonstrate with Southern blot and chromosomal in situ hybridization experiments using cDNA clones that the genes coding for the α subunits of the leukocyte adhesion receptors are located on the short arm of chromosome 16, clustered between bands 16p11 and 16p13.1, a region involved in rearrangements in myelomonocytic leukemia cells (16). Similarly, the leukocyte receptors’ common β subunit has been mapped to chromosome 21, band q22, which has recently been identified as a breakpoint in translocations associated with the blast phase of chronic myelogenous leukemia (17).

Materials and Methods

DNA. The production of the mouse X human hybrids has been described elsewhere (15). The hybrids, as well as the mouse thymoma BW5147 cells, were grown in RPMI 1640 medium supplemented with 20 mM L-glutamine, 50 µM 2-ME, 50 µg/ml gentamicin, and 20% FCS. DNA was extracted from the hybrids, BW5147, and human hairy leukemia cells by standard procedures (18).

Southern Blot Analysis. Aliquots of 10 µg of Eco RI-digested DNA from the different cells were electrophoresed in a 1% agarose gel and blotted overnight onto nylon membranes (Zetaprobe; Bio-Rad Laboratories, Richmond, CA) using 0.4 N sodium hydroxide. The membranes were prehybridized with 6 X SSC (0.6 M sodium chloride, 0.06 M sodium citrate), 1% SDS, 10 mM EDTA, 0.5% dehydrated nonfat milk, and 100 µg/ml of herring sperm DNA for 12 h at 65°C, and were probed either with a 1.2-kb Eco RI–Bam H1 fragment from the LFA-1α cDNA clone (Larson, R. S., et al., manuscript in preparation), a 1.0-kb Eco RI fragment from a Mac-1α cDNA clone (Corbi, A. L., et al., manuscript in preparation), or a 1.2-kb Eco RI–Pst I fragment from the p150,95 α cDNA clone (5), labeled by nick translation (18). Membranes were washed in 1 X SSC, 0.2% SDS at 65°C and exposed to preflashed XAR-5 film for 24 h with intensifying screen.

Chromosomal In Situ Hybridization. Metaphase chromosomes were prepared from peripheral blood lymphocytes of normal human males and in situ hybridization performed as previously described in detail (19). The probes were tritium labeled by nick translation to a specific activity of 9.2 × 10⁶ cpm/µg (p150,95α), 1.0 × 10⁷ cpm/µg (LFA-1α), 1.43 × 10⁷ cpm (Mac-1α), and 1.6 × 10⁷ cpm/µg (LFA-1/Mac-1/p150,95 β) using the four [³H]dNTPs. Metaphase spreads were visualized with a combination of incident fluorescent and transmitted visible light. Identification of the specific chromosomes was carried out by Q-banding using quinacrine mustard dihydrochloride.

Results

Chromosomal Location of the Three α Subunit Genes. Somatic cell hybrids have been previously obtained by fusion of the PHA blasts of a human LAD patient or maternal control with the HGPRT-deficient murine thymoma cell line BW5147 (P X BW and M X BW hybrids, respectively) (15). Immunofluorescence cell sorting was used to isolate hybrids positive or negative for the human
LFA-1 α or β subunits. Those hybrids positive for the human LFA-1 α subunit express it noncovalently associated with the murine β subunit on the cell surface. The Mac-1 and p150,95 α subunits are not expressed by these hybrids, as is usually the case for T lineage cells. Karyotyping and analysis of chromosome 16-specific markers on the different cells localized the LFA-1α subunit gene to chromosome 16 (15). To determine whether the genes coding for the α subunits of Mac-1 and p150,95 were also located on chromosome 16, DNAs from these human X mouse somatic cell hybrids were subjected to Southern hybridization with LFA-1, Mac-1, and p150,95 α subunit cDNA probes (Fig. 1). Human X mouse somatic cell hybrids expressing the LFA-1α subunit (M X BW α+ and P X BW α+) were positive for the presence of the three α subunit genes. Two DNA fragments of 10 and 8 kb were detected when the LFA-1α cDNA probe was hybridized to the DNA from the somatic cell hybrids digested with Eco RI (Fig. 1 A, lanes 4 and 8). A single 15-kb Bam HI genomic fragment was observed in the same hybrids using the Mac-1α-specific probe (Fig. 1 B, lanes 4 and 8). The p150,95α subunit cDNA probe hybridized to a 6.0-kb Eco RI fragment in DNA derived from LFA-1α+ cells (Fig. 1 C, lanes 3 and 7). The somatic cell hybrid DNAs were analyzed in parallel with genomic DNA from human hairy leukemia cells and from the murine cell line BW5147 (Fig. 1). In each case, the human genomic DNA yielded bands of the same size as those observed with the hybrids, while no band was detected on mouse DNA, demonstrating the human origin of the genomic fragments hybridizing to the different probes. Moreover, the authenticity of the bands detected by the p150,95α and the LFA-1α probes was further confirmed by genomic cloning, since cosmid clones isolated from a human genomic DNA library using the same cDNA probes exhibit the same pattern of hybridization (data not shown).

Karyotype analysis of the human LFA-1α-expressing hybrids M X BW α+ and P X BW α+ has previously shown that they contain only two human chromosomes in common, 16 and X (15). The other hybrids lacked the LFA-1α subunit and chromosome 16, but contained the X chromosome encoding HGPRT. These hybrids showed no hybridization with the LFA-1α, Mac-1α, and p150,95α cDNA probes (Fig. 1 A and B, lanes 3, 5, 6, and 7, and Fig. 1 C, lanes 4, 5, 6, and 8). Therefore, only the presence of human chromosome 16 was concordant with the detection of genomic fragments hybridizing to LFA-1, Mac-1, and p150,95 α-specific probes. These results strongly suggest that the α subunits of the leukocyte adhesion receptors LFA-1, Mac-1, and p150,95 are encoded by genes located on chromosome 16.

Position of the α Subunit Genes within Chromosome 16. To locate more precisely the genes for the α subunits within chromosome 16, chromosomal in situ hybridization was performed on human peripheral blood lymphocytes, with the same cDNA probes used for the Southern blot studies (Fig. 2). In every case, >90 metaphases were analyzed and the total number of counted grains exceeded 160. In the case of the LFA-1α subunit, 8.3% of the grains (15/177) were located on chromosome 16, and 4.5% (8/177) specifically appeared on the band 16p11 (Figs. 2 and 3). The Mac-1 α–specific probe rendered 14.2% of the grains (32/225) on chromosome 16, 6.2% (14/225) located on the band 16p11, and 8.4% (19/225) between bands 16p11 and 16p13.1. For the α subunit of
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FIGURE 1. Southern hybridization of leukocyte adhesion receptors α subunit probes to human–rodent somatic cell hybrids, human, and mouse genomic DNA. Aliquots of 10 μg of Eco RI–digested DNA from the hybrid cell lines P × BW α+, P × BW α−, M × BW β+, M × BW β−, M × BW α+, M × BW α−, the parental mouse BW5147 cell line, and human hairy leukemia cells were probed with fragments from the LFA-1 α subunit (A), Mac-1α subunit (B), and p150,95 α subunit (C) cDNA clones. Hind III–cut λ DNA markers are indicated.
p150,95, 15.2% of the grains (26/164) localized to the chromosome 16, and 9.8% were found between bands 16p11 and 16p13.1. Taken together, these data locate the genes coding for the α subunits of the leukocyte adhesion receptors to a very close region on the short arm of chromosome 16, between bands 16p11 and 16p13.1, demonstrating the existence of a leukocyte adhesion α subunit gene cluster.

Mapping of the Gene Encoding the Leukocyte Adhesion Receptor Common β Subunit. Somatic cell hybrid studies have previously located the gene for the LFA-1/Mac-1/p150,95 β subunit to chromosome 21 (15, 20, 21). We have used the isolated β subunit cDNA clone to determine the position of the gene within chromosome 21. Analysis of 182 counted grains from 86 metaphases showed that 6.6% of the grains (12/182) appeared on chromosome 21 (Fig. 2), and all of them were located on band 21q22 (Fig. 3), demonstrating that the β subunit of LFA-1, Mac-1, and p150,95 maps to 21q22.

Discussion

In the present paper we report the location of the genes encoding the α and β subunits of the leukocyte adhesion receptors LFA-1, Mac-1, and p150,95. The three α subunit genes map to the short arm of chromosome 16 (bands 16p11–16p13.1), probably centromeric to the α-globin genes (22), to a region where no genetic marker was previously available. The location of the three genes demonstrates the existence of a cluster of at least three genes involved in cellular adhesion. The gene encoding the common β subunit has been localized on chromosome 21, band 21q22.

The arrangement of the leukocyte adhesion receptor α subunit genes may have implications for the regulation of their expression. The total synthesis of the three leukocyte adhesion receptor α subunits must be coordinated with synthesis of the common β subunit for assembly of the α/β complex. In addition, the expression of the α subunits of Mac-1, LFA-1, and p150,95 is regulated during leukocyte differentiation (23); the level of Mac-1 and p150,95 are reversed during the maturation of blood monocytes (Mac-1 > p150,95) into tissue macrophages (p150,95 > Mac-1), and Mac-1 and p150,95 α expression can be triggered in several cell lines by inducing them to differentiate (23, 24).

Analysis of the primary structure of the leukocyte adhesion receptors has evidenced their relationship to the ECM receptors, a group of α/β heterodimers involved in the attachment of cells to their environment via the recognition of the sequence Arg-Gly-Asp (RGD) within their ligands (8). Overall, the α subunits of the leukocyte adhesion receptors are 25% homologous to the rest of the ECM receptor α subunits (12–14), while the leukocyte receptor β subunit is 45% identical to the ECM receptor β subunits (10, 11). The relationship between both groups of receptors has defined a superfamily of proteins involved in cellular adhesion termed integrins (9). Three families have been defined within the integrin gene superfamily, each with a unique β subunit: the fibronectin receptor/VLA family (sharing β1), the leukocyte adhesion receptors (sharing β2), and the vitronectin receptor/platelet IIb/IIIa subfamily (sharing β3). The α subunits of the ECM receptors (sharing either β1 or β3) exhibit 45% identity among them, independently of the β subunit they associate with. Therefore, the α subunits of
LFA-1, Mac-1, and p150,95 are more closely related among themselves than to the ECM receptor α subunits, reflecting the presence of structural and functional features unique to the leukocyte adhesion receptors. The genes coding for LFA-1α (A), Mac-1α (B), p150,95α (C), and the common β subunit (D) are located on chromosomes 16 and 21. Major peaks are observed on the short arm of chromosome 16 (A-C) and on the long arm of chromosome 21 (D). No secondary peaks are observed with any of the probes.

**Figure 2.** Distribution of the silver grains over metaphase chromosomes after hybridizing with the probes for LFA-1α (A), Mac-1α (B), p150,95α (C), and the common β subunit (D). Major peaks are detected on the short arm of chromosome 16 (A-C) and on the long arm of chromosome 21 (D). No secondary peaks are observed with any of the probes.
for a number of integrin α subunits have been mapped; the genes for VLA-1α and VLA-2α appear on chromosome 5 (25), while those for VLA-3α and the platelet glycoprotein IIb are located on chromosome 17 (25, 26). The presence
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Figure 3. Composite silver grain distribution on human chromosomes 16 and 21 after in situ hybridization using the LFA-1 (A), Mac-1 (B), and p150,95 (C) α-specific probes, and the common β subunit probe (D). Each dot represents a grain.

of structural features unique to the leukocyte adhesion receptor α chains (5; Corbi, A. L., et al; Larson, R. S., et al., manuscripts in preparation) and their greater relationship to one another than to the two ECM receptor integrin subfamilies correlates with the proximity of their genes on 16p11–16p13.1.

In addition to its function as a cell adhesion molecule on monocytes and granulocytes, the leukocyte receptor Mac-1 exhibits iC3b-binding ability, and has been designated the complement receptor type 3 (CR3) (1). p150,95 also functions as a receptor for iC3b (27, 28). The complement receptors type 1 and 2 (CR1, CR2) share the capacity to bind C3-derived fragments and belong to a large family of structurally related proteins involved in the regulation of complement activation, which maps to chromosome 1 (29, 30). Mac-1 and p150,95 are unrelated to CR1 and CR2 in structure (5; Corbi, et al., manuscript in preparation). Thus, from an evolutionary point of view, both in terms of structural homology and chromosomal location, Mac-1 and p150,95 are more akin to other adhesion molecules than to other complement receptors.

The region where the leukocyte adhesion receptor α subunit gene cluster maps has been implicated in chromosomal abnormalities in acute myelomonocytic leukemia (AMMoL) patients (16). 25% of AMMoL patients exhibit chromosomal rearrangements such as an inversion of chromosome 16, inv(16)(p13;q2), and less frequently, a reciprocal translocation of both chromosomes 16, t(16;16)(p13;q22), and in both cases, morphologically abnormal bone marrow eosinophils have been detected. Le Beau et al. (16) have determined that the breakpoint on 16q22 is located within the metallothionein (MT) gene cluster and that the aberrant rearrangement splits the MT gene cluster, part of which is relocated at 16p13. Additional chromosomal abnormalities in AMMoL patients [t(1;16;16)(q32;p13;q22)] have suggested that the junction distal 16p13-proximal q22 is the critical gene rearrangement. Le Beau et al. (16)
have hypothesized that transcriptional control elements of the MT gene cluster could be translocated to the short arm of chromosome 16 by inversion, thus acting on a gene located on 16p13. The localization of the leukocyte adhesion receptor α subunit cluster to 16p11–p13.1 raises the possibility of its involvement in these chromosomal rearrangements. If the leukocyte adhesion receptors regulate cell differentiation, as already demonstrated for other integrins (31), the presence of adventitious control elements within the gene cluster might alter the normal differentiation program of the cell, leading to further proliferation. Alternatively, the control elements of any of the leukocyte receptors α subunit genes might be involved in these chromosomal rearrangements, activating a gene on 16q22. Interestingly, we note that the site of rearrangement on chromosome 1 in the complex t(1;16;16) is the location of a multigene family that includes CR1 and CR2 (30).

In parallel studies, we have mapped the gene encoding the leukocyte receptor common β subunit to chromosome 21, band 21q22, thus localizing the defect in LAD disease. Studies using chromosome 21 deletion mutants and linkage of restriction fragment length polymorphisms map the β subunit to 21q22.3, in agreement with our data (Stewart, G. D., R. E. Tanzi, T. K. Kishimoto, M. J. Buraczynska, H. Drabkin, J. F. Gusella, T. A. Springer, D. M. Kurnit, and M. L. Van Keuren, manuscript in preparation). The band 21q22 has been identified as a breakpoint in chromosomal translocations [t(3;21)(q26;q22)] associated with the blast phase of chronic myelogenous leukemia (CML), leading to the suggestion that it may be related to progression of CML (17). Further studies are required to determine whether parts of the α or β subunit genes are involved in the DNA rearrangements detected in AMMoL and CML patients, respectively.

Summary

The adhesion receptors Mac-1, LFA-1, and p150,95 are cell surface α/β heterodimers that play a key role in leukocyte adhesion processes. The genes for Mac-1, LFA-1, and p150,95 α subunits have been located to chromosome 16 by means of Southern blot analysis using a series of somatic cell hybrids. Chromosomal in situ hybridization has demonstrated that the genes for the three α subunits map to the short arm of chromosome 16, between bands p11 and p13.1, defining a cluster of genes involved in leukocyte adhesion. The gene encoding the LFA-1/Mac-1/p150,95 β subunit, and defective in leukocyte adhesion deficiency, has been located on chromosome 21, band q22. The leukocyte adhesion receptor α and β subunits are mapped to chromosomal regions that have been shown to be involved in cytogenetic rearrangements in certain patients with acute myelomonocytic leukemia and the blast phase of chronic myelogenous leukemia, respectively.

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