Constitutive Overexpression of the L-Selectin Gene in Fresh Leukemic Cells of Adult T-Cell Leukemia That Can Be Transactivated by Human T-Cell Lymphotropic Virus Type 1 Tax

By Makoto Tatewaki, Kazunari Yamaguchi, Masao Matsuoka, Toshinori Ishii, Masayuki Miyasaka, Shigeo Mori, Kiyoshi Takatsuki, and Toshiki Watanabe

L-selectin is an adhesion molecule of the selectin family that mediates the initial step of leukocyte adhesion to vascular endothelium. Upon cellular activation, expression of the L-selectin gene is downregulated at both the protein and mRNA levels. To understand the mechanism of leukemic cell infiltration into organs, we studied the expression and regulation of L-selectin mRNA in fresh leukemic cells of adult T-cell leukemia (ATL) patients and investigated the response of the L-selectin promoter to human T-cell lymphotropic virus type 1 (HTLV-1) Tax, which is a viral transcriptional activator. Flow cytometry showed that L-selectin was expressed on fresh ATL cells along with other activation antigens. Northern blot analysis showed that ATL cells overexpressed the L-selectin mRNA and that the level was aberrantly upregulated after PMA stimulation. Studies using in situ hybridization showed expression of the L-selectin mRNA in the infiltrating leukemic cells in the liver of two ATL patients. Intravenous injection of a rat T-cell line that overexpresses L-selectin showed increased organ infiltration. The induction of Tax expression in JPS9 cells resulted in about a twofold increase in the mRNA expression levels compared with the basal level. Chloramphenicol acetyltransferase (CAT) assay after transient cotransfection showed about a fivefold transactivation of the L-selectin promoter by Tax. The serum level of the shed form of L-selectin was significantly increased in ATL patients (mean ± SD, 4,215.4 ± 4,111 ng/mL) compared with those of asymptomatic carriers and healthy blood donors (mean ± SD, 1,148.0 ± 269.0 ng/mL and 991.9 ± 224 ng/mL, respectively). These results indicated that ATL cells constitutively overexpress the L-selectin gene that can be transactivated by HTLV-1 Tax. The overexpression of L-selectin, as well as of inflammatory cytokines, by ATL cells may provide a basis for ATL cells to attach the vascular endothelium, leading to transmigration and organ infiltration.

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Address reprint requests to Toshiki Watanabe, MD, PhD, Department of Pathology, The Institute of Medical Science, The University of Tokyo, Tokyo; the Second Department of Internal Medicine, Kumamoto University School of Medicine, Kumamoto; and the Division of Organ Bioregulation, Biomedical Research Center, Osaka University Medical School, Osaka, Japan. Submitted December 30, 1994; accepted June 5, 1995.

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Address reprint requests to Toshihiko Watanabe, MD, PhD, Department of Pathology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108, Japan.

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transactivation. In addition to the viral genes, Tax induces the expression of the cellular transcription factor genes that are controlled by transmembrane signals and also some genes that encode cytokines and their receptors. Some of the genes that can be transactivated by Tax are constitutively expressed in ATL cells that modulate clinical features. ATL cells have a membrane phenotype of activated CD4+ T cells, expressing interleukin-2 receptor α (IL-2Ra), HLA-DR, and other activated cell antigens. The data of Ishikawa et al. suggested that ATL cells are characterized as CD4+ Leu-8+ T cells. Because Leu-8 antigen is identical to L-selectin, ATL cells express typical activation antigens and L-selectin at the same time, which suggests that the regulation of L-selectin expression is aberrant.

We studied the expression of L-selectin in ATL cells and tested the regulation of its gene expression by HTLV-1 Tax, which would provide a clue to understanding the molecular mechanism of L-selectin gene expression and leukemic cell infiltration into various organs in ATL patients.

MATERIALS AND METHODS

**Patients plasma and cell samples.** ATL was diagnosed according to the described criteria. Briefly, a T-lymphocyte neoplasm that resulted from the monoclonal expansion of HTLV-1-infected T cells was diagnosed as ATL. Seropositivity against HTLV-1 was tested using a PA kit (Fujirebio, Tokyo, Japan) and confirmed using an enzyme immunoassay (EIA) kit (Eizai, Tokyo, Japan). The integration of HTLV-1 provirus DNA was studied using Southern blotting.

Peripheral blood mononuclear cells (PBMCs) from patients with ATL and normal blood donors were isolated by density gradient centrifugation with Ficoll Paque (Pharmacia, Uppsala, Sweden). RNA was immediately extracted from the cells or they were quickly frozen in liquid nitrogen and stored at −80°C until use. Plasma samples were collected at the time of PBMC preparation and stored at −80°C until use.

**Cell lines.** Jurkat is a human T-cell line established from T-ALL cells and JPX-9 is a derivative of Jurkat cells carrying the transfected Tax gene under the control of metallothionein promoter. MT-1 is a human T-cell line derived from leukemic cells of an ATL patient. These cells were cultured in RPMI1640 supplemented with 10% fetal bovine serum and antibiotics. FL cells were derived from human amnion cells and maintained in Dulbecco’s modified Eagle’s medium supplemented with 5% fetal bovine serum and antibiotics. The expression of Tax in JPX9 cells was induced by adding 20 μmol/L CaCl₂ into the medium.

**Immunophenotyping.** Cell surface markers of leukemic cells from 20 patients with ATL (13 with acute type and 7 with chronic type) were studied and those of normal T cells from 9 blood donors served as controls. Heparinized whole blood samples were immunophenotyped without PBMC isolation. Cell surface antigens were detected by standard immunofluorescence using a panel of directly fluorescein isothiocyanate (FITC)- or phycoerythrin-conjugated monoclonal antibodies. The expression of surface antigens was studied by means of double immunofluorescence using antibodies that react with CD3, CD4, CD8, CD25, and Leu-8 (Becton Dickinson, San Jose, CA; Coulter, Hialeah, FL). Double immunofluorescence was performed using a Spectrum III flow cytometer (Ortho, Westwood, MA). A total of more than 5,000 cells were analyzed for each sample.

Immunohistochemical analysis of the formalin-fixed and parafin-embedded tissues was performed using SAB method. The expression of the vanadyl ribonucleoside complex. To study the modulation of gene expression, PBMC samples were cultured for 18 to 24 hours with or without phorbol myristate acetate (PMA; 10 ng/mL) and then cytoplasmic RNA was extracted. Ten micrograms of total RNA was Northern blotted. After transfer to nylon membranes (BioDyne B; Pall BioSupport Corp, Glen Cove, NY), the RNA was fixed by UV irradiation. The membrane was hybridized with probes at 42°C in a solution containing 50% formamide, 4× SSC, 10× Denhardt’s solution, 0.1% sodium dodecyl sulfate (SDS), and 100 μg/mL of denatured salmon sperm DNA. An L-selectin cDNA probe covering entire protein coding sequence was prepared using reverse transcription-polymerase chain reaction (RT-PCR) and cloning into the pcRII plasmid by means of TA cloning (In Vitrogen, San Diego, CA). The nucleotide sequence of the insert cDNA was confirmed by sequencing using the Sequenase kit (US Biochemicals, Cleaveland, OH).

For detection of L-selectin mRNA in tissue samples, we performed in situ hybridization. Samples of the formalin-fixed and parafin-embedded liver of two ATL patients and a biopsy specimen of a patient with chronic active hepatitis were used for the study. Serial sections of 4 to 6 μm were prepared on the slides coated with 3-aminoethylpolyethiloxilysine. Digoxigenin-labeled antisense and sense L-selectin cRNA probes were prepared from a plasmid containing 589bp cDNA fragment (nucleotide position 998-1586) using DIG RNA Labelling Kit (Boehringer Mannheim Biochemica, Mannheim, Germany).

**RNA isolation.** Expression of L-selectin by the transformed cell line was confirmed by Northern blotting and flow cytometry (data not shown). About 1 × 10⁸ cells of the L-selectin-overexpressing TARL-2 [TARL-2 (L+)] and the original cell line were labeled by FITC and injected into KWAH rat intravenously. Two hours after injection, an immunobiochemical study was performed using anti-FITC antibody (DAKO PATTES A/S, Glostrup, Denmark) and SAB method.
OVEREXPRESSION OF L-SELECTIN IN ATL

### Table 1. Leu-8 Expression in the Peripheral Blood of ATL Patients and Normal Controls

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<th>Case No.</th>
<th>Type</th>
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<td>54.0</td>
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The percentages of positive cells for each antigen are shown.

**Abbreviations:** CD4⁺, Leu-8⁺, percentages of cells positive for respective antigen among lymphocytes; Leu-8⁺/CD4⁺, percentage of Leu-8⁺-positive cells among CD4⁺ cells; acute, acute-type ATL; chronic, chronic-type ATL; control, control samples collected from normal volunteers; ND, not determined.

* MFI of positive cells was lower than that of control cells.

Using an sL-selectin enzyme-linked immunosorbent assay (ELISA) kit (Bender MedSystems, Vienna, Austria) and those of the soluble form of IL-2Ra (sIL-2Ra) were quantified with an sIL-2Ra ELISA kit, according to the manufacturer's instructions. The plasma or serum samples numbered 29 from ATL patients, 10 from asymptomatic carriers, and 10 from seronegative control individuals. Among the samples from ATL patients, PBMCs from 5 were included in the analysis of L-selectin mRNA expression using Northern hybridization.

### RESULTS

**The surface expression of L-selectin on ATL cells.** Flow cytometry showed that the percentage of L-selectin-positive cells among those that were CD4⁺ was 65.7% ± 17.6% (mean ± SD) in ATL patients, whereas that of the normal control was 36.5% ± 6.15% (mean ± SD; Table 1). The results of the flow cytometry are summarized in Fig 1. The percentage of Leu-8⁺-positive cells among the CD4⁺ cells that almost represents the entire leukemic cell population was significantly high in ATL patients (P = 0.0002 by Mann-Whitney U test).

**L-selectin mRNA expression in ATL cells.** Northern blotting showed that normal PBMCs expressed L-selectin transcripts at a relatively high level and that the PBMCs of ATL patients, which consisted of mainly ATL cells, expressed it at much higher levels (Fig 2). These results were confirmed in all 8 patients with ATL that were studied. We then tested the modulation of gene expression of L-selectin by activating the cells in vitro. The level of L-selectin expression in the ATL cells was upregulated after 18 to 24 hours of stimulation with PMA, whereas the normal PBMCs were downregulated (Fig 3). All of the three HTLV-I viral transcripts, ie, genomic, env, and pX, were detected after stimulation, whereas they were not expressed in fresh leukemic cells at a detectable level (Fig 3). Thus, fresh primary ATL cells constitutively expressed L-selectin.
The induction of L-selectin gene expression by Tax in JPX-9 cells. To examine the effect of Tax on the L-selectin gene expression, we used JPX-9 cells that have an inducible Tax gene. We studied the time course of the expression of L-selectin and Tax by means of Northern blotting. CdCl₂ added to the culture medium induced Tax gene expression in JPX-9 cells within 1.5 hours. Although L-selectin gene is constitutively expressed in JPX-9 cells at a relatively high level, the expression started to increase along with the induction of Tax expression. It showed a small peak at 2 hours, a small decrease at 6 hours, and then a continuous increase until 33 hours, reaching about double the basal level (Fig 6). CdCl₂ did not influence the level of L-selectin gene expression in the parental Jurkat cells (data not shown). Thus, the results suggested that Tax increased the transcription of the L-selectin gene and that endogenous cellular factors are involved in the induction.

The L-selectin promoter is transactivated by HTLV-1 Tax. To examine whether the L-selectin promoter, which we identified (Tatewaki et al, submitted for publication), responds to Tax, we assayed CAT by means of transient cotransfection with the Tax expression vector. The reporter plasmid, pLS-1 CAT, has the L-selectin promoter fragment up to -885. The promoter was activated by Tax both in Jurkat and FL cell lines. Representative results are shown in Fig 7. The magnitude of transactivation by Tax was about fivefold in FL cells and a little less in Jurkat cells.

To identify the Tax-responsive element(s), we prepared CAT reporter plasmids with a serially deleted promoter sequence and tested the response to Tax. However, the levels of transactivation were gradually decreased with deletion and no specific region that affected the response was identified (data not shown). These results suggested that multiple elements in the promoter are involved in the transactivation by Tax.

Elevated serum levels of sL-selectin in ATL patients. To examine the overexpression of L-selectin by ATL cells in vivo, we measured the level of sL-selectin in the sera of 29 ATL patients, 10 asymptomatic carriers, and 10 normal blood donors. We also measured the serum level of IL-2Rα, which is a good marker of leukemic cell mass in vivo. The mean level of sL-selectin in 29 patients with ATL was significantly increased (mean ± SD, 4,215.4 ± 4,111 ng/mL) compared with those in asymptomatic carriers and normal blood donors (mean ± SD, 1,148.0 ± 269 ng/mL and 991.9 ± 224 ng/mL, respectively; Fig 8). We studied the correlation between sL-selectin and sIL-2Rα in samples from 25 patients with ATL. As shown in Fig 9, the level of sL-selectin correlated well with that of sIL-2Rα (γ = 0.6), suggesting that the serum level of sL-selectin depends on the leukemic cell mass. These results provided more evidence that L-selectin is overexpressed by ATL cells in vivo.

DISCUSSION

The adhesion properties of peripheral blood leukemic cells from 10 patients with ATL have been characterized by Ishikawa et al. They showed that E-selectin and vascular cell adhesion molecule-1 (VCAM-1) mediate ATL cell adhesion to endothelial cells. However, the counter-receptors on ATL cells for E-selectin and VCAM-1 remained to be determined.
Adhesion molecules expressed on ATL cells have not been well characterized. Fukudome et al.\textsuperscript{14} reported that intercellular adhesion molecule-1 (ICAM-1) expression was highly induced in human T cells transformed by HTLV-1 and fresh ATL cells. However, it is not known whether they are involved in organ infiltration of ATL cells. Thus, further characterization of adhesion molecules expressed on ATL cells should help understand the mechanism underlying organ infiltration.

We showed that the L-selectin gene is constitutively overexpressed in ATL cells and that the viral transactivator Tax can induce its expression. We also showed that the serum levels of sL-selectin in ATL patients were significantly elevated and that they correlated well with those of sIL-2Rα. These results indicated that the constitutive overexpression of L-selectin is one of the characteristic phenotypes of ATL cells.

Our flow cytometric study of surface markers of ATL...
cells clearly showed that they expressed Leu-8 antigen (Table 1 and Fig 1). The mean fluorescence intensity (MFI) of positive cells was generally low in ATL cells compared with that of normal controls. Considering the constitutive overexpression of mRNA shown in this study, low MFI may suggest a rapid turnover of the protein. In line with this notion, other investigators have reported variable levels of L-selectin expression on ATL cells. It has been reported that L-selectin surface expression is downregulated by various leukocyte isolation procedures, which may explain some inconsistency in the data reported by different groups. Therefore, to characterize the L-selectin expression, mRNA expression should be studied by such means as Northern blotting in addition to flow cytometry and immunocytochemistry. The results of our Northern blot analysis showed a rather constant and high level of mRNA expression in ATL samples (Fig 2), which is consistent with the results of our flow cytometric analysis. In addition, demonstration of L-selectin mRNA in the infiltrating cells in the liver of ATL patients (Fig 4), but not in the liver with inflammatory infiltration of lymphocytes, appears to provide more evidence for abnormal regulation of gene expression, because it was reported that L-selectin expression was downregulated after extravasation.

Subsets of CD4+ T cells that showed enhanced transendothelial migration were identified as CD29high, CD45ROhigh, and CD45RA-50. These phenotypes are similar to those of ATL cells. In addition to this, the overexpression of L-selectin may render ATL cells more sticky to vascular endothelial cells than normal T cells. Furthermore, ATL and HTLV-1–infected cells produce various inflammatory cytokines.52-54 These phenotypic characteristics of ATL cells would enable them to activate vascular endothelial cells to express adhesion molecules and to attach themselves firmly to activated endothelium. The notion that overexpression of L-selectin itself can affect the lymphocyte recirculation seems to be partly supported by our observation that a rat T-cell line that overexpresses L-selectin showed an increased

Fig 6. Induction of L-selectin mRNA expression after the expression of HTLV-1 Tax in JPP9 cells. (A) Results of Northern blot hybridization. Samples of 10 μg total RNA were subjected for formalin-agarose gel electrophoresis. (B) The relative intensities of the hybridization signals. Measured radioactivity was corrected using that of GAPDH.

Fig 7. Transactivation of the L-selectin gene promoter by HTLV-1 Tax. Representative results of a CAT assay after the cotransfection of pLS-1 CAT and a Tax expression vector in FL cells (A). The percentage of conversion of chloramphenicol that is corrected by the β-Gal activity is shown in (B). The CAT activity was transactivated about fivefold in the presence of Tax.
level of organ infiltration when injected into a rat intravenously (Fig 5). However, Schleiffenbaum et al have shown that the increased levels of sL-selectin in the medium inhibited the interaction between L-selectin and its ligands. Therefore, it appears more likely that, even though ATL cells might have enhanced capacity to adhere to and transmigrate the endothelial cells, organ infiltration is determined by the dynamic balance in vivo between the increased stickiness of ATL cells and the inhibitory effect of sL-selectin in the serum. Thus, to understand the biologic significance of the L-selectin overexpression, the correlation between the serum levels of sL-selectin and the clinical manifestation of organ infiltration in ATL patients of each clinical subtype should be further studied, and the gene expression of other adhesion molecules as well as inflammatory cytokines should be characterized.

As mentioned before, HTLV-1 Tax induces expression of cytokines, growth factors, and their receptors, IL-2Rα and parathyroid hormone-related protein (PTHrP) are examples of these genes, and they are constitutively overexpressed in ATL cells. The overexpression of cellular genes that can be transactivated by Tax is one of the common features of ATL cells. The L-selectin gene appears to be the first example of adhesion molecules with this characteristic.

The level of transactivation of the L-selectin promoter induced by Tax was about fivefold in repeated experiments, which is lower than that of reported cellular genes. This difference could be explained by the relatively high level of background activity of L-selectin promoter both in Jurkat cells and FL cells (Fig 6). Similar observations were recently reported by Ohbo et al on the IL-2Rγ chain gene expression that was transactivated by HTLV-1 Tax. It may also be due to the difference in the molecular mechanism underlying the transactivation. It has been shown that HTLV-1 Tax transactivates gene expression through interactions with cellular transcription factors such as CREBP, NF-κB, and SRF. No consensus sequence elements for these factors were found in the L-selectin promoter up to −885 bp. Instead, there are multiple sequence elements for Ets family oncogenes (Tatewaki et al, submitted for publication), which reportedly participate in the transactivation of HTLV-1 LTR and the promoter of the PTHRp gene. Functional characterization is now under way to answer whether these characteristics of the L-selectin promoter could explain the apparent difference in the response to Tax.

In all the ATL samples that we have so far examined, viral mRNAs were not detected using Northern blotting. Furthermore, our RT-PCR studies of fresh primary ATL cells from 25 patients could not detect pX mRNA in more than half of them. The amplification of the pX mRNA was very weak in the remaining samples and it corresponded to a level of 1 viral mRNA expressing cell among $1 \times 10^5$ negative cells (Watanabe et al, unpublished observations). Thus, we could not exclude the possibility that the amplified pX mRNA was expressed in nontransformed HTLV-1–infected cells that contaminated the samples. It was also shown that nearly half of the ATL patients have defective provirus that lacks 5′ regions in their tumor cells (Matsuoka et al, unpublished observation). These results indicated that the L-selectin gene is constitutively overexpressed in the absence of HTLV-1 Tax in vivo. This finding implies that there is another mechanism independent of HTLV-1 Tax underlying the overexpression of L-selectin in fresh ATL cells. The
same notion could be applied to other Tax-responsive genes such as IL-2Ra, PTHrP, and transforming growth factor β that are overexpressed in fresh ATL cells.

In conclusion, we showed the constitutive overexpression of the L-selectin gene in ATL cells in vivo that can be transactivated by HTLV-1 Tax that provided another clue to understanding the pathogenesis of organ infiltration of ATL cells.

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Constitutive overexpression of the L-selectin gene in fresh leukemic cells of adult T-cell leukemia that can be transactivated by human T-cell lymphotropic virus type 1 Tax

M Tatewaki, K Yamaguchi, M Matsuoka, T Ishii, M Miyasaka, S Mori, K Takatsuki and T Watanabe