T3 Surface Molecules on Adult T Cell Leukemia Cells Are Modulated In Vivo

By Masao Matsuoka, Toshio Hattori, Tohru Chosa, Hiroyuki Tsuda, Shigeki Kuwata, Mitsuaki Yoshida, Takashi Uchiyama, and Kiyoshi Takatsuki

Cells from eight patients with adult T cell leukemia (ATL) and from four patients with non-ATL were examined to see if the T3 antigen of these cells could be modulated in vitro. We found a low density of T3 antigen and the presence of Tac antigen on cells from all patients with ATL. The density of T3 antigen on non-ATL was normal, and Tac antigen was not detected. Modulation of T3 antigen and an increase in Tac antigen-positive cells occurred when cells from patients with T4 non-ATL were cultured with OKT3 monoclonal antibody (mAb). Those changes in T3 antigen density and the appearance of Tac antigen-bearing cells by OKT3 mAb were not so marked when ATL cells were used. But the modulation of T3 antigen and the increase in Tac antigen-bearing cells by OKT3 mAb were closely related in cells from six ATL patients. These findings suggest that T3 and Tac antigen receptor complexes on ATL cells are not functionally “frozen” by leukemic changes and might be modulated in vivo. In addition, modulation of T3 surface antigen on ATL cells was not induced by cultivation with human T cell leukemia virus type 1 particles and envelope proteins obtained by gene technology.

MATERIALS AND METHODS

Reagents. Fluorescein isothiocyanate (FITC)-conjugated OKT3, T4, and T8 mAbs and unlabeled OKT3, T4, and T8 mAbs were purchased from the Ortho Pharmaceutical Co (Raritan, NJ). FITC-conjugated anti-Tac mAb was generated as described elsewhere. FITC-labeled goat (Fab)2 antihouse (Fab)2 fragments of immunoglobulin G (IgG) was from Cappel Laboratories (Cochraneville, Pa). Affinity-purified FITC-labeled goat (Fab)2 antihuman IgG was from Tago Inc (Burlingame, Calif). Concanavalin A (Con A) was from Pharmacia (Uppsala, Sweden) and phorbol 12-myristate 13-acetate (PMA) was from Consolidated Midland (Brewster, NY).

Cell culture and cell lines. All cell cultures were done in complete medium, RPMI 1640 (Nissui, Tokyo) containing 10% fetal bovine serum (GIBCO, Grand Island, NY), 100 U/mL of penicillin, 100 µg/mL of streptomycin, and 2 mmol/L L-glutamine. Cell counts and viabilities were determined visually with trypan blue. The MT-2 cell line cells were kindly provided from Dr I. Miyoshi (Kochi Medical University, Kochi, Japan). HUT 102 cell lines were from Dr R.C. Gallo (National Cancer Institute, Bethesda, Md). Peripheral blood mononuclear cells from patients and ten healthy donors (aged 26 through 38) were separated from heparinized blood by Ficoll-Conray density-gradient centrifugation. Normal T cells were purified by sheep red blood cell rosette-forming methods. After being washed three times with phosphate-buffered saline (PBS), cells were cultured with or without various reagents in a humid atmosphere with 5% CO2 at 37°C. For short-term culture, recombinant interleukin 2 (IL 2), which was kindly provided by Dr J. Hamuro (Ajinomoto Pharmaceutical, Yokohama, Japan), was used. Cells were fed with IL 2 (1 U/mL) every two days.

Patients. Diagnoses of patients were based on accepted criteria for clinical, hematologic, and laboratory findings. Antibody to ATL virus-associated antigens (anti-ATLA-Ab) in the sera was measured by indirect immunofluorescence (IF) as described by Hinuma et al, using MT-1 cells. Antibodies to virus-associated cell surface membrane antigens (anti-MA-Ab) were also measured, using HUT 102 cells as described by Robert-Guroff et al. Briefly 50 µL of 1:100 diluted patient’s sera was added to 106 cells and incubated for 30 minutes on ice. After washing twice with PBS containing 1% bovine serum albumin (BSA) and 0.1% sodium azide (NaNO3), 50 µL
of FITC-conjugated affinity-purified antihuman IgG (1:40 dilution) was added. Cells were washed twice after another 30 minutes of incubation on ice and analyzed by a laser flow cytometry system (Spectrum III/Ortho Diagnostic Systems, Westwood, Mass) with exposure to a laser light of 488 nm at the intensity of 50 mW as described previously.11 The results were expressed as the relative proportions of IF-positive cells. Detection of human T cell leukemia/lymphotropic virus type I (HTLV-I) proviral DNA has been performed using a provirus clone, ATK-1, as a source of the probe.12,13

Isolation of HTLV-I particles and envelope protein of HTLV-I. HTLV-I particles were obtained from 2 L of culture medium of MT-2 cells as described by Yoshida et al11 with a slight modification. Briefly, HTLV-I particles were obtained by centrifugation at 25,000 rpm for 90 minutes in a Hitachi RP 42 rotor after removing cell debris by low centrifugation (2,000 rpm for ten minutes). Crude HTLV-I particles were suspended in TNE buffer (20 mmol/L Tris HCl, pH 7.5/100 mmol/L NaCl/1 mmol/L EDTA), layered on a sucrose density gradient (20% to 60%), and centrifuged for 18 hours at 25,000 rpm in the rotor. For analysis of viral proteins, aliquots of each fraction were subjected to 15% polyacrylamide slab gel electrophoresis as described by Laemmli.14 A low-molecular-weight kit from Pharmacia was used for molecular weight markers. Proteins were stained by silver staining methods. Fractions that contained virus proteins were collected, dialyzed against PBS, and stored at −70 °C until use. The concentration of virus is arbitrarily set as described below; 1 unit of virus equals 1071 (A260).

Envelope protein of HTLV-I was obtained by transforming Escherichia coli strain JK1046 with plasmid PEH9. The protein was purified as described previously.15

Cell surface marker analyses. Cell surface markers were analyzed by a laser flow cytometry system as described. Malignant cells were cultured in 24-well tissue culture plates (Linbro Flow Lab, McLean, Va) at a concentration of 2 × 10^6 cells per milliliter in a total volume of 1 mL. OKT3 mAb (which was dialyzed against PBS for 18 hours at 4 °C), PMA, and Con A were added at various concentrations. After 18 hours of culture, T3 and Tac antigens were examined by indirect and direct IF methods.11,12 For direct IF assay, the cutoff point was determined for each sample at which 0.5% of non-stained cells were positive, and the percentage of IF-positive cells was determined. Cells cultured with IL 2 were examined using the same system. The saturating amount of antibodies was determined using T8-positive chronic lymphocytic leukemia cells (T-CLL) for the OKT3 mAb indirect IF system and HUT 102 cells for the TAC mAb direct IF system.

RESULTS

Patients. Clinical profiles of the patients are presented in Table 1. Sera from all ATL patients were positive and those from non-ATL patients were negative for both anti-ATLA-Ab and anti-MA-Ab. Proviral DNA was demonstrated in all ATL cells and not detected in non-ATL cells. The diagnoses of chronic or acute ATL were based on clinical profiles as described elsewhere.16 Surface phenotype analyses of cells immediately after cell separation showed that all ATL cells were T3+, T4+, T8+, Tac+; cells from patients MG, NB, and IT were T3+, T4+, T8+, Tac-; cells from patient ST were T3+, T4-, T8+, Tac-. The relative proportions of malignant cells in cell suspensions were assessed either by OKT4 or OKT8 mAb. More than 90% of cells from patients with ATL and T4 non-ATL reacted with OKT4 mAb, and 94% of cells from patient ST reacted with OKT8 mAb. The viability of cells immediately after cell separation was more than 95% and that of cultured cells was more than 90% except for cells cultured with PMA (10^-4 mol/L); 62% to 90% of these were viable. Cell surface marker analyses of fresh cells are listed in Table 2. All ATL cells expressed Tac antigen and a low MFI of T3 antigen; however, apparent relationships between two markers were not observed. The proportions of all malignant cells bearing T3 antigen and the MFI of T3 antigen did not change significantly during culture for 18 hours in complete medium. The MFI of T3 antigen on ATL cells and on the other malignant cells was 29 to 56 and 77 to 95, respectively (Figs 1A, 2A, and 3A).

Modulation of T3 antigen and induction of Tac antigen of non-ATL cells. In the presence of OKT3 mAb (150 ng/mL), MFI of T3 antigen on normal cells decreased by 74% and those of non-ATL cells decreased by 28% to 54%, depending on the cells (Figs 1A and 4). The relative proportions of T3 antigen-bearing cells decreased by 74%, but those of non-ATL cells decreased only by 2% to 22% (Fig 1B). We also studied OKT4 or OKT8 mAb (150 ng/mL) to deter-

<table>
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<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration (mol)</th>
<th>WBC (x 10^9/L)</th>
<th>Anti-ATLA-Ab</th>
<th>Anti-MA-Ab (%)</th>
<th>Proviral DNA</th>
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<td>MG</td>
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<td>M</td>
<td>T4-ML (leukemic)</td>
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<td>16.9</td>
<td>—</td>
<td>4</td>
<td>—</td>
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<td>60</td>
<td>M</td>
<td>T4-CLL</td>
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<td>—</td>
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<td>98</td>
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<td>22</td>
<td>11.1</td>
<td>+</td>
<td>100</td>
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ML, malignant lymphoma; CLL, chronic lymphocytic leukemia; ATL, adult T cell leukemia; anti-ATLA-Ab, antibody to ATL virus-associated antigens; anti-MA-Ab, antibody to membrane-associated antigens.
Stimulation with OKT3 mAb, even after cultivation with medium, and did express it after not expressing Tac antigen significantly cells did slightly decreased the MFI of Tac antigen on NB T4 cells and other mitogens on T3 antigen density were examined. Con A IL2 leukemic cells expressed Tac antigen only in the presence of cells were viable after cultivation. The non-ATL 90% of the phenomenon was also observed in cells from ST, in which 1072 MATSUOKA ET AL PMA markedly decreased those on all cells (Fig IA). This with these mAbs did not change in reactivity with OKT3, using T4 (from MG) and T8 (from ST) cells. Cells cultured whether these mAbs modulated mine I T4, T3, or T8 antigens, using T4 (from MG) and T8 (from ST) cells. Cells cultured with these mAbs did not change in reactivity with OKT3, OKT4, or OKT8 mAbs (data not shown). The effects of other mitogens on T3 antigen density were examined. Con A slightly decreased the MFI of T3 antigen on NB T4 cells and PMA markedly decreased those on all cells (Fig 1A). This phenomenon was also observed in cells from ST, in which 90% of the cells were viable after cultivation. The non-ATL cells did not express Tac antigen significantly (0% to 7%), even after cultivation with medium, and did express it after stimulation with OKT3 mAb. Con A, or PMA; and T8 leukemic cells expressed Tac antigen only in the presence of PMA (Figs 1B and 4). MFI and Tac antigen-positive cells also increased in the presence of mitogens used (Fig 1A). In general, the decrease in MFI of T3 antigen was well-correlated with the increase of relative proportions of Tac antigen-bearing cells. Cells cultured with HTLV-I did not change their reactivities to T3 and Tac mAbs at all.

**Modulation of T3 antigen and expression of Tac antigen on ATL cells.** The results of acute ATL and chronic ATL are shown in Figs 2 and 3, respectively. The changes in MFI of T3 antigen on ATL cells by OKT3 mAb were not as great as those of non-ATL cells (Figs 2A, 3A, and 4). In particular, cells from patient SW did not significantly decrease in MFI of T3 antigen when cultured with OKT3 mAb (Figs 2A and 4). The subtle changes in MFI of T3 antigen on ATL cells could not be attributed to contamination with normal T cells because cells from patient IH, whose peripheral blood leukocyte counts were highest and whose percentage of T4-bearing cells was 96%, had the greatest change in MFI of T3 antigen caused by OKT3 mAb (Fig 2A). In contrast to the non-ATL malignant T cells, changes in MFI of T3 antigen on ATL cells by Con A did not occur. The viabilities of ATL cells cultured with PMA (10^-8 mol/L) were 62% to 82% and the percentage of Tac antigen-bearing cells decreased (Fig 2B), but MFI of Tac antigen-positive cells increased (Figs 2A and 3A). Tac antigen was expressed, to a variable extent, on all ATL cells immediately after cell separation, and the proportions of Tac antigen-positive cells increased after 18 hours of culture (Table 2, Figs 2B and 3B). The enhancement of ATL Tac antigen-bearing cells and increase in MFI of them by OKT3 mAb were also slight as compared with non-ATL but were evident. Cells from SW,

### Table 2. Cell Surface Markers of Fresh Leukemic Cells

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<tr>
<th></th>
<th>T3 (%)</th>
<th>MFI</th>
<th>T3 (%)</th>
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<td>48.1</td>
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*Indicates reactivity to OKT8 mAb.

![Fig 1. T3 and Tac antigen expression of non-ATL cells after cultivation with various agents. (A) Mean fluorescence intensity of T3 and Tac antigen. (B) Percentage of T3 and Tac antigen-positive cells. Cells were cultured with complete medium, and OKT3 mAb (150 μg/mL), Con A (4 μg/mL), or PMA (10^-8 mol/L) for 18 hours. After cultivation, cells were stained with OKT3 or anti-Tac mAb and analyzed by flow cytometry. (□), T3 antigen; (○), Tac antigen.](http://www.bloodjournal.org)
whose T3 antigen was not modulated by OKT3 mAb, again
did not react with OKT3 mAb with respect to an increase in
T3 antigen-bearing cells but, rather, MFI of Tac antigen
decreased. T3 antigen on T1 cells could be modulated by
OKT3 mAb; however, the significant increase of Tac anti-
gen-positive cells was not observed (Fig 3B). When the cells
from six other patients whose T3 antigen was moderately
modulated by OKT3 mAb (NK, IH, NT, AS, KT, and EF)
were examined, the increases in the percentage of Tac
antigen-bearing cells and their MFI caused by OKT3 mAb
were evident (Figs 2 and 3). Therefore, these two phenom-
ena, the modulation of T3 antigen and the expression of Tac
antigen, are closely related, and T3–Ti complex activation
can mediate Tac antigen expression on most ATL cells. This
suggests that T3 antigen on ATL cells is already modulated
in vivo by unknown agents.

**T3 and Tac antigens on cultured neoplastic cells.** T3
and Tac antigens were examined using cells cultured with IL
2. ATL cells from three patients (NT, TI, AS), non
ATL
cells from three patients (NB, MG, ST), and normal T cells
from three individuals were studied. MFI of T3 antigen
increased continuously in all cells examined until day 7,
although the percentage of positive cells did not increase (Fig
5). At day 14, decrease in MFI of T3 antigen was observed
in one of the ATL cells examined. Interestingly, the percentage
of T3* cells decreased at day 14 in case TI. Percentage of
Tac antigen-bearing cells and its MFI on ATL cells con-
tinued to increase and reached maximum at day 14 (Fig 6).
A subtle increase of Tac antigen-bearing cells was observed

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**Fig 2.** T3 and Tac antigen expression of ATL cells after
cultivation with various agents. Mean fluorescence intensity (A)
and percentage of antigen-positive cells (B) in acute ATL. (•), T3
antigen; (○), Tac antigen.

**Fig 3.** T3 and Tac antigen expression of ATL cells after
cultivation with various agents. Mean fluorescence intensity of T3
antigen (A) and percentage of Tac antigen-positive cells (B) of
chronic ATL cells.
at day 7, when non-ATL cells and normal peripheral blood lymphocytes were used. But the increase was not so marked.

**Effect of HTLV-I particles and envelope protein on T3 antigen modulation.** It was proposed that leukemogenesis is receptor mediated and that retrovirus interacts with immunospecific or growth receptors of neoplasms.20,21 So we examined the effects of HTLV-I particles on T3 antigen modulation and Tac antigen expression on all ATL cells. ATL cells were cultured with HTLV-I particles at concentrations of 0.2 to 0.01 U/mL for 18 hours; 0.2 U/mL was chosen as the highest concentration because it saturates HTLV-I receptors on ATL cells as examined by FITC-HTLV particles (unpublished observations, November 1984). At all concentrations, we did not see any significant changes in T3 antigen expression or the expression of Tac antigen on ATL cells from seven cases caused by HTLV-I particles (Figs 2 and 4). We also cultured cells from three patients with ATL (NT, TI, AS) with envelope gene products that have been proven to have antigenicity recognized by serum from ATL patients.18 The concentrations of envelope protein used were 30, 10, and 3 μg/mL. None of these experiments showed changes of T3 and Tac antigens in any sense. Simultaneously, ATL cells from the same three cases were cultured with 10% patient's serum, which was known to contain antibodies against HTLV-I envelope protein,18 for seven days to determine whether the serum may prevent the binding of viruses to ATL cells, resulting in the increased expression of T3 antigen. However, the cells cultured with the serum did not change their reactivities to T3 and Tac mAb as compared with medium cultured cells (data not shown).

**DISCUSSION**

We previously reported that the MFI of T3 antigen on ATL cells is low compared with normal T and T8-CLL cells.11 Here we have shown that malignant T4 cells from three patients whose sera did not contain anti-ATLA-Ab and whose cells did not have proviral DNA of HTLV-I had the normal density of T3 antigen on their surfaces. T3 antigen on ATL cells was relatively resistant to modulation by OKT3 mAb, although T3 antigen on the non-ATL malignant cells was modulated by OKT3 mAb. In addition, the expression of Tac antigen and the marked increase in Tac antigen-positive cells after culture in complete medium were specific to ATL cells. Non-ATL malignant T4 cells expressed Tac antigen modulation of T3 antigen by mAb or after stimulation by mitogens in 18-hour culture.

The expression of Tac antigen and the low density of T3 antigen on ATL cells suggest that T3–T1 on ATL cells may be continuously stimulated by unknown agents in vivo. McGrath et al.20,21 proposed the receptor-mediated leukemogenesis hypothesis because murine leukemia virus (MuLV)-
induced thymic lymphoma specifically bound FITC-MuLV, whereas only 0.5% to 2% of normal thymocytes bound them. In this view, the leukemogenic retrovirus express envelope antigens that allow the virus to bind and infect the rare subset of thymic lymphocytes that express receptors complementary to these viral antigens. Thus, it was speculated that slowly transforming retroviruses would interact with immunospecific or growth receptors on the surface of B- and T-cell neoplasms to cause continued rounds of mitogenesis.

Zanders et al. reported that the peptides of influenza virus proteins induce the loss of T3 antigen on the surface of cloned T cells specific for influenza virus in 18-hour culture. Therefore, we investigated the effect of HTLV-I particles on the expressions of T3 and Tac antigens on ATL cells to determine whether T3-Ti antigen interacts with HTLV-I protein. The T3 antigen of these cells was not modulated, and there was no enhancement of the expression of Tac antigen on cultivation with HTLV-I particles.

The results indicate that the T3-Ti-mediated leukemogenesis hypothesis for ATL cells is less likely. But it is also possible that ATL cells are already tolerant to HTLV-I or other antigens as is suggested by the low density of T3 antigen. Alternatively, envelope protein of HTLV-I may be fragile and cannot react with T3-Ti complexes. Thus we used envelope gene products of HTLV-I. Again, no changes in cell surface markers were observed.

It is difficult to interpret the increase of MFI of T3 antigen on cultured ATL cells as well as on non-ATL and normal T cells after cultivation. Increase in MFI of T3 antigen on cultured ATL cells could not be attributed to the selective proliferation of cells that had high density of T3 antigen because it is well known that ATL cells do not proliferate in the presence of IL 2.23

There were no differences between acute and chronic ATL cells in our system. However, ATL cells are different from non-ATL T4 malignant cells in MFI of their T3 antigen and in the conditions by which Tac antigen could be induced. Waldmann et al. recently reported that ATL cells were Tac positive, whereas most HTLV-negative Sézary cells were Tac negative. Tsudo et al. reported that Tac antigen on ATL cells could not be modulated (down-regulation) by anti-Tac mAb, although Tac antigen on Con A-stimulated T cells could be modulated, and proposed that abnormal expression of Tac antigen might play a key role in proliferation of ATL cells. Here we could see increase of MFI or the percentage of Tac antigen-bearing cells by OKT3 mAb as well as PMA, suggesting that Tac antigen on ATL cells were not frozen and could be regulated (up-regulation) by appropriate stimuli. Yodoi et al. recently reported a novel lymphokine (ATL-derived factor) that increases the expression of Tac antigen on a human natural killer cell line. A number of other receptors are also related to growth of cells, including transferrin receptor. We have recently observed that transferrin receptors on ATL cells are modulated as those on normal activated T cells (T.U., unpublished observations, August 1984).

Nevertheless, the decrease in MFI of T3 antigen and the expression of Tac antigen were specific to ATL. The expression of Tac antigen on ATL cells was enhanced by T3 mAb stimulation. Thus specific expression of Tac antigen on ATL cells might be the result of the continuous stimulation of T3-Ti complexes in vivo by unknown agents.

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M Matsuoka, T Hattori, T Chosa, H Tsuda, S Kuwata, M Yoshida, T Uchiyama and K Takatsuki

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