Autocrine growth stimulation of a human T-cell lymphoma line by interleukin 2

(interleukin 2 receptor/growth regulation)

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Communicated by André Lwoff, July 1, 1985

ABSTRACT The ability of tumor cells to produce and to respond to their own growth factor (autocrine secretion) may be of importance for their growth. We describe a human tumor cell line regulated by an autocrine secretion of the growth factor interleukin 2 (IL-2). This T-lymphocyte cell line, IARC 301, was established from a patient with a T-cell lymphoma in the absence of any added specific growth factor. It constitutively expresses biologically functional high-affinity cell-surface receptors for IL-2 as shown by the binding of both radiolabeled purified IL-2 and monoclonal antibodies to IL-2 receptors. In addition, it synthesizes IL-2, which is bound to cell surface receptors. Monoclonal antibodies directed against either IL-2 or the IL-2 receptor block IARC 301 cell growth. These findings demonstrate that the proliferation of this tumor cell line is mediated by an autocrine pathway involving endogenous IL-2 production and its binding to cell surface receptors.

Tumor cells often do not need growth factors that control normal cell division. Such observations suggest that growth factors might play an essential role in the development of malignancies. This hypothesis is supported by the evidence that some oncogenes code for growth factors or growth factor receptors (1–4).

Activation of an autocrine self-stimulation, whereby a cell both secretes and responds to a growth factor (5), may be of importance for the growth of some tumors and cell lines. This was first described for cells infected with transforming viruses, which secrete transforming growth factors able to support normal cell growth in soft agar and induce tumorigenicity of those cells (6–8).

More recently, it has been reported that cells transformed with simian sarcoma virus synthesize a polypeptide, required for their growth, which is the product of the viral oncogene v-sis and exhibits biological activities of platelet-derived growth factor (PDGF) (9, 10). Also an osteosarcoma cell line expresses PDGF receptors and produces a PDGF-like growth factor (11). Finally, viral oncogenes of the src family can induce chicken myeloid cells to produce a chicken myelomonocytic-like growth factor that stimulates their proliferation (12).

Interleukin 2 (IL-2) or T-cell growth factor (13, 14), a glycoprotein of molecular weight 15,500, is released by T lymphocytes after stimulation by an antigen or a mitogen and allows the long-term growth in vitro of normal T cells (15, 16). It promotes the growth of T lymphocytes through specific cell surface receptors that appear upon activation (17) and are expressed transiently after such a stimulation (18). The gene coding for human IL-2 has been cloned (19–21), and IL-2 can be purified either by recombinant DNA techniques or from the supernatant of activated human T cells.

Some human T-cell leukemia virus type I (HTLV-I)-transformed T-cell lines initially established in vitro in the presence of IL-2 have become independent of this factor, respond to IL-2, and synthesize it (22), although most HTLV-I-transformed cell lines do not (23). This suggests that IL-2 might stimulate growth of some tumor T-cell lines by an autocrine mechanism.

We have established a human T-cell line IARC 301 from the lymph nodes of a patient with a malignant lymphoma. This cell line, which has never been grown in the presence of IL-2, bears IL-2 receptors on its surface. In this work we asked whether an autocrine stimulation by IL-2 could be involved in IARC 301 cell growth.

We show that IARC 301 cells constitutively express high-affinity receptors for IL-2 to which are bound IL-2 molecules that had been produced by these cells themselves. That the cells require their own receptors and IL-2, which they synthesize themselves in order to grow, is demonstrated by the fact that antibodies against IL-2 or against the receptor inhibit cell proliferation. An autocrine stimulation by IL-2 is obviously involved in the growth of this cell line.

MATERIALS AND METHODS

Cells and Monoclonal Antibodies. IARC 301 cell line was derived from the lymph nodes of a patient with high-grade malignant non-Hodgkin T-cell lymphoma (unpublished data). The cell line, initially established in vitro in the presence of irradiated human fibroblasts, MRC5, is now cultured without feeder cells in RPMI medium supplemented with 10% heat-inactivated fetal calf serum and 2 mM L-glutamine and without addition of a specific growth factor. In standard long-term culture conditions, cell concentration is maintained between 1 × 10^5 and 1.3 × 10^6 cells per ml. IARC 301 cells were consistently shown to be free of mycoplasma.

The human T-cell lines CEM and 1301 were obtained from J. Strominger and M. Fellous, respectively. The human T-cell line Jurkat was obtained from A. M. Schmidt-Verhulst, and the murine IL-2-dependent cell line CTL-2 was subcloned in our laboratory.

Anti-IL-2 monoclonal antibodies DMS1 and DMS3 (24) were given by K. Smith. DMS1 antibody was partially purified from ascitic fluid by ammonium sulfate precipitation. Anti-IL-2 receptor antibody, called anti-Tac (ascitic fluid) (25, 26), was a gift of W. Greene, and B1.49.9 (ascitic fluid) (27) was given by M. Hemler. Control IgG1 IDA 17 and IgG2a AIDA 10.9, BALB/c anti-idiotype antibodies, were obtained from P. Legrain, and W6/32, an anti-HLA antibody, was from Dr. Owen. OKT3 was purchased from Ortho Diagnostics, and anti-transferrin receptor antibody 5E9 came from the American Tissue Culture Collection.

Abbreviations: IL-2, interleukin 2; PDGF, platelet-derived growth factor; HTLV, human T-cell leukemia virus.

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Radioimmunoassay. Fifty microliters of cells (3 x 10^5) were incubated with 50 μl of monoclonal antibodies in RPMI medium containing 20 mM Hepes, 0.8% bovine serum albumin, and 0.1% azide (pH 7.2) at various dilutions for 2 hr at 4°C. Then they were washed twice, and 50 μl (10^6 cpm) of 125I-labeled rabbit anti-mouse Ig F(ab')2 fragment (Amersham) was added for 2 hr at 4°C. Then the cells were washed three times, and radioactivity was assayed in a γ counter.

IL-2. Biosynthetically titrated and unlabelled human IL-2 were prepared from the supernatant of the Jurkat culture medium as described by Robb et al. (17) and purified by using a DMS3-immunoaffinity column (24). By gel electrophoresis and autoradiography, this IL-2 preparation appeared to be pure. In addition, its binding could be blocked by a 100-fold excess of unlabelled recombinant IL-2 (Amer, Thousand Oaks, CA).

Recombinant human IL-2 (Amergen) and IL-2 purified from phytohemagglutinin-stimulated human lymphocytes (Collaborative Research, Waltham, MA) were used when specified.

IL-2 Bioassay. IL-2 bioactivity was determined by the proliferation of the murine IL-2-dependent CTLL-2 line (28). Cells (10^4) were incubated in 0.2 ml of RPMI medium containing 5% fetal calf serum, 2 mM L-glutamine, 10 mM Hepes, and 50 μM 2-mercaptoethanol for 24 hr, and 0.5 μCi (1 Ci = 37 GBq) of [3H]thymidine was added for the last 4 hr of culture. One unit of IL-2 per ml, 0.12 ng/ml as determined for recombinant IL-2, gives 50% of maximum proliferation in this assay and is equivalent to 1.5 IL-2 "Reference Reagent units" as defined by the Biological Response Modifiers Program of the National Cancer Institute. To inhibit IL-2 activity, purified DMS1 antibody was added together with 0.8 unit of IL-2 per ml at the beginning of the assay as described (24).

IL-2 Binding Assay. The binding of radiolabeled IL-2 was performed by using published procedures (17). In brief, the cells were incubated at 37°C and washed before the binding assay as described. Binding of IL-2 was then performed for 2 hr at 4°C. Nonspecific binding was determined by adding a 100-fold excess of unlabelled IL-2, either purified from the Jurkat supernatant or recombinant IL-2, and was <10% of specific binding at all IL-2 concentrations in both cases.

Acid pH Elution of Cell Surface-Bound Proteins. Cell surface-bound proteins were eluted by published procedures (29). In brief, 1.4 x 10^6 exponentially growing IARC 301 cells, or 4.5 x 10^6 CEM or 1301 cells, were washed twice in Dulbecco's phosphate-buffered saline at 4°C and resuspended in 10 ml of 0.2 M glycine-HCl buffer at pH 2.8. After a 10-min incubation at 4°C, the cells were centrifuged, and the supernatant was neutralized to pH 7 and filtered on a YM-5 membrane (Amicon) in order to equilibrate it in phosphate-buffered saline and to concentrate it to a final volume of 0.6 ml.

IARC 301 Proliferation and Growth Assays. Exponentially growing cells were washed twice in Dulbecco's phosphate-buffered saline, resuspended in RPMI medium containing 10% fetal calf serum and glutamine, and distributed in triplicate samples in a 96-well round-bottom plate (0.2 ml per well) at cell concentrations between 2.5 x 10^4 and 2 x 10^5 cells per ml. After incubation for various times in humidified 95% air/5% CO2 at 37°C, 0.5 μCi of [3H]thymidine was added for 5 hr, and the cultures were harvested on glass-fiber filters. In some experiments, instead of measuring [3H]thymidine incorporation, live cells were counted by trypan blue exclusion at the end of the culture. When indicated, IL-2 or antibodies were added at the beginning of the culture.

RESULTS

A human cell line, IARC 301, was derived from the lymph nodes of a patient with a T lymphoma. This cell line, initially established in the presence of irradiated human fibroblasts as the feeder layer, was then grown in vitro for several months in RPMI medium supplemented with 10% fetal calf serum in the absence of feeder cells and of any added growth factor. IARC 301 cells were tested for the presence of retroviruses by reverse transcriptase assay, and the result was consistently negative. This cell line is OKT9+, OKT11+, WT1* (30), OKT3−, OKT4+, OKT6−, OKT8+, B1−, surface immunoglobulin-negative, and Fc receptor-negative.

IARC 301, a Human T-Cell Line, Expresses Receptors for IL-2 Constitutively. The expression of IL-2 receptors on the cell surface of IARC 301 was demonstrated by radioimmunoassay with anti-IL-2 receptor antibody B1.49.9 as the first antibody and 125I-labeled (Fab')2 fragments from sheep anti-mouse antibodies as the second antibody (Fig. 1); the same result was obtained with anti-Tac antibody. More than 90% of exponentially growing IARC 301 cells were shown to express IL-2 receptors on their surface by indirect immunofluorescence with anti-receptor B1.49.9 antibody (not shown).

Two types of IL-2 receptors have been shown to be present on T cells (31): high-affinity receptors, responsible for the biological activity (17, 32), and low-affinity receptors. Both kinds of receptors are recognized by B1.49.9 and anti-Tac antibodies. Because low-affinity receptors are usually much more abundant than high-affinity receptors (31, 33), the binding of antibodies is not sufficient to detect the expression of biologically functional high-affinity receptors. In order to demonstrate the presence of high-affinity receptors for IL-2, biosynthetically titrated, purified IL-2 was used. Fig. 2 shows the binding curve of IL-2 to IARC 301 cells. By Scatchard analysis of the same data, it could be calculated that there are about 2800 binding sites for IL-2 per cell with a Kd of 8 x 10^−12 M. This Kd is comparable to the values we obtained for high-affinity IL-2 binding sites on human peripheral blood lymphocytes activated for 3 days with phytohemagglutinin and to published data (31).
These results show that IARC 301 cells grown in vitro in the absence of an exogenous source of IL-2 bear on their surface high-affinity receptors for IL-2.

IARC 301 Can Respond to Exogenous IL-2. Under standard culture conditions where IARC 301 cells were seeded at 2 × 10^6 cells per ml, growth of IARC 301 did not require exogenous IL-2. However, at lower cell concentrations where the cells grew poorly or did not grow, IL-2 allowed cell growth (Table 1). The effect of IL-2 on cell growth at low density also was measured as a function of time in culture by [3H]thymidine incorporation into cellular DNA (Fig. 3). Both proliferation, as measured by [3H]thymidine incorporation, as early as 2 days after addition of IL-2 and cell recovery after 6 days of culture showed that IL-2 receptors on IARC 301 cells are biologically functional and that these cells require IL-2 in order to grow at low densities.

IARC 301 Produces IL-2. IARC 301 cells bear biologically functional IL-2 receptors, and addition of IL-2 to the culture medium improves cell growth. These data suggest that they may produce this factor themselves.

To test for the secretion of IL-2 by IARC 301 cells, the culture supernatant was concentrated about 25 times by ammonium sulfate precipitation (50–80% fraction; ref. 22). The concentrated supernatant induced the proliferation of CTLL-2 cells and contained 0.6 units of IL-2 per ml; no IL-2 could be detected in the concentrated supernatant of two control cell lines, CEM and 1301. Thus, IARC 301 cells secrete IL-2 in their culture medium. It previously has been shown that treating cells bearing IL-2 on their receptors at acid pH (below 4) removes IL-2 from the receptors (22). We used this method to test the presence of IL-2 on IARC 301 cell surface. The material eluted from exponentially growing IARC 301 cells by acid pH treatment promoted the proliferation of the IL-2-dependent CTLL-2 line, whereas the material eluted from two control human T-cell lines, CEM and 1301, did not (Fig. 4 Inset). Monoclonal anti-IL-2 antibody

Table 1. Growth of IARC 301 cells with and without exogenous IL-2

<table>
<thead>
<tr>
<th>IL-2</th>
<th>Cells × 10^3 per ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>+</td>
<td>0.5</td>
</tr>
<tr>
<td>-</td>
<td>0.25</td>
</tr>
<tr>
<td>+</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The cells were seeded initially between 0.25 and 2 × 10^6 cells per ml in 0.2 ml as described in the absence (−) or presence (+) of 20 units of recombinant IL-2 per ml, and the cell concentration was measured at day 2, 3, or 6. ND, not measurable because the culture was overgrown causing cell death.

Fig. 2. Binding of [3H]IL-2 to IARC 301 cells. Binding of [3H]IL-2 was performed at 4°C as described.

Fig. 3. [3H]Thymidine incorporation of IARC 301 at low cell concentration. IARC 301 cells were cultured at 5 × 10^6 cells per ml without IL2 (○), with 20 units of purified human IL-2 per ml from phytohemagglutinin-stimulated blasts (A), or with 20 units of recombinant IL-2 per ml (■) for various periods of time. [3H]Thymidine was added to the culture for the last 5 hr of incubation.

Fig. 4. Neutralization of the biological activity eluted from IARC 301 cells by anti-IL-2 antibodies. Dilutions of purified antibody DMS1 (●) or control IgG1 (■) were mixed with the biological activity eluted from IARC 301 cells at 0.8 units/ml. As a control, 0.8 units/ml of recombinant IL-2 (♂) were mixed with serial dilutions of DMS1 antibody (maximum thymidine incorporation was 10,000 cpm). CTLL-2 cells were then added and treated thereafter as for an IL-2 bioassay. (Inset) Titration of the IL-2 activity eluted from IARC 301 (♂) and two control cell lines, CEM (○) and 1301 (○), at acid pH was done by using the IL-2 bioassay as described.
were pulsed with culture is five IgG and ammonium sulfate Anti-IL-2 if IL-2 which binds 6/32, of the following of anti-Tac growth that previously are necessary that 301 cells were seeded at 2 x 10^5 cells per ml on day 0 without added exogenous IL-2 in the presence of anti-Tac antibody (ascitic fluid, dilution 10^-2), control IgG2 (ascitic fluid, dilution 10^-2), and anti-HLA antibodies W6/32 (ascitic fluid, dilution 10^-2), and the cell concentration was measured on days 2, 3, 4, and 5.

DMS1 (24) inhibited both the proliferation of CTLL-2 due to the material eluted from IARC 301 and the proliferation due to recombinant IL-2 (Fig. 4), confirming that IL-2 is eluted from IARC 301 cell surface. It can be calculated from the results presented in Fig. 4, that this would correspond to about 650 molecules of IL-2 bound per cell on exponentially growing IARC 301.

Anti-IL-2 Receptor Antibodies Inhibit IARC 301 Growth. Since IARC 301 produces IL-2 and has on its surface functional IL-2 receptors, we wondered if in standard culture conditions (without addition of exogenous IL-2) IL-2 receptors are necessary for cell growth. It has been shown previously that the anti-IL-2 receptor antibody anti-Tac inhibits growth of IL-2-dependent T-cell lines (26). The effect of anti-Tac antibody on IARC 301 proliferation was studied by adding anti-Tac antibody to IARC 301 cultures and by following cell growth. As shown in Table 2, anti-Tac antibody inhibited IARC 301 proliferation, whereas an unrelated antibody of the same subclass and an anti-HLA antibody, W 6/32, which binds to IARC 301 cell surface as seen by immunofluorescence, at the same dilution of ascites fluid had little effect.

Inhibition of IARC 301 proliferation by anti-Tac establishes that functional IL-2 receptors are necessary for IARC 301 cells to grow.

Anti-IL-2 Antibodies Inhibit IARC 301 Growth. We next tested if IL-2 synthesized by IARC 301 is necessary for its growth. Anti-IL-2 antibody DMS1, partially purified by ammonium sulfate precipitation, was added to IARC 301 culture and [3H]thymidine incorporation was measured 2 days later. DMS1 added at a final concentration of 200 µg/ml inhibited >90% of the cell proliferation (Table 3). A control purified IgG of the same subclass at the same concentration had very little effect. Cell growth also was followed for 5 days by adding DMS1 antibody at day 0. Under these conditions, after 5 days of culture, most of the cells grown in the presence of anti-IL-2 were dead at all concentrations, while control cells had grown normally (Table 3). These experiments demonstrate that IL-2 produced by IARC 301 is required for its growth.

DISCUSSION

It has been suggested that an autocrine mechanism (5) may control the growth of tumor cells; this is based on the fact that some tumor cell lines produce a growth factor and respond to it. In this paper, we demonstrate such an autocrine growth mechanism for a growth factor controlling T lymphocyte proliferation, IL-2. We have established a human tumor T-cell line IARC 301, which has always been grown in vitro in the absence of IL-2. Our data show that it constitutively expresses receptors for IL-2 as measured both by the binding of anti-receptor antibodies and by the binding of radiolabeled purified IL-2. IL-2 is also synthesized by these cells as shown by elution at acid pH of IL-2 from their surface. Exponentially growing IARC 301 cells bear about 2800 IL-2 receptors free of IL-2 on their surface, and it is estimated that about 650 molecules of IL-2 could be eluted from the surface receptors; altogether the number of surface receptors is estimated to be about 3400. About 20% of the receptors seem to carry IL-2 at any time; this value may be higher considering that the number of IL-2 molecules is probably underestimated. Such an occupancy level supports a physiological role of IL-2 for the growth of IARC 301. The fact that the cells produce IL-2 and bear receptors for IL-2 suggests that they may need this growth factor in order to grow. The autocrine action of IL-2 in IARC 301 cells is directly demonstrated by the ability of anti-IL-2 antibodies as well as anti-receptor antibodies to inhibit cell growth. It is worth noting that if IARC 301 cells are grown in the presence of anti-IL-2 receptor antibodies, about 30 times more IL-2 can be found in their growth medium 2 days later, than in the medium of cells grown without antibodies (not shown). This indicates that the cells normally use up the IL-2 they secrete and that the IL-2 uptake is inhibited by anti-receptor antibodies. All these data show that the cell surface receptors for IL-2 present on IARC 301 cells and IL-2 synthesized by these cells control their autocrine growth stimulation.

IARC 301 was established from a tumor, and it is most likely that because of its origin this cell line is clonal. However, to rule out the possibility that the cells producing IL-2 and those responding to it might be different, we have cloned IARC 301. One of the clones was studied in more detail: its growth is inhibited by anti-Tac and DMS1 antibodies as well as the cell line, and IL-2 could be eluted at acid pH from its surface (not shown).

Nothing is known in the cases of autocrine growth about how the ligand and receptor interact and induce cell growth: the ligand might bind to cell surface receptors and then behave as an exogenous ligand, or it might bind to the receptor at some intracellular location, somewhere along the pathway that secreted and membrane proteins follow. The ability of anti-IL-2 antibodies to completely block IARC 301 growth indicates that, in this case, the ligand interacts with cell surface receptors, which is in favor of the former hypothesis.

To our knowledge, IARC 301 is the only human tumor T-cell line that has been initially established in vitro in the absence of exogenous IL-2 and that expresses functional IL-2 receptors. Its autocrine growth system may be responsible for its in vitro growth whether or not autocrine growth plays any role in vivo in neoplastic conversion.

Table 2. Inhibition of IARC 301 cell growth by anti-IL-2 receptor antibody

<table>
<thead>
<tr>
<th>Antibody added</th>
<th>Cells × 10^5 per ml</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4.9</td>
<td>10.3</td>
<td>15.0</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Anti-Tac</td>
<td>2.3</td>
<td>3.3</td>
<td>4.5</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Control IgG2</td>
<td>4.2</td>
<td>10.0</td>
<td>16.0</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>W6/32</td>
<td>4.0</td>
<td>9.6</td>
<td>11.0</td>
<td>21.0</td>
<td></td>
</tr>
</tbody>
</table>

IARC 301 cells were pulsed with added exogenous IL-2 in the presence of purified DMS1 or control purified IgG1 (200 µg/ml). Two or five days later the cell concentration was measured, or the cells were pulsed with [3H]thymidine. ND, not measurable because the culture is overgrown causing cell death.

Table 3. Inhibition of IARC 301 cell growth and [3H]thymidine incorporation by anti-IL-2 antibody

<table>
<thead>
<tr>
<th>Antibody added</th>
<th>Cells × 10^5 per ml</th>
<th>[3H]Thymidine incorporation, cpm × 10^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Day 2</td>
<td>Day 5</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>8.4</td>
</tr>
<tr>
<td>DMS1</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Control IgG1</td>
<td>2</td>
<td>8.0</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>3.9</td>
</tr>
<tr>
<td>DMS1</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Control IgG1</td>
<td>1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

IARC 301 cells were cultured without added exogenous IL-2 in the presence of purified DMS1 or control purified IgG1 (200 µg/ml). Two or five days later the cell concentration was measured, or the cells were pulsed with [3H]thymidine. ND, not measurable because the culture is overgrown causing cell death.
In a previous study, Gootenberg et al. (22) have shown that two HTLV-I-transformed T-cell lines, which had been established in vitro in the presence of IL-2 and which were adapted to grow in medium lacking this factor, produce IL-2 and proliferate in response to exogenous IL-2. Also, a gibbon ape cell line MLA-144 has been described that expresses IL-2 receptors and secretes IL-2 (34). This suggests that these cells might autostimulate their growth. IARC 301 cells not only express IL-2 receptors and secrete IL-2, but also their growth is inhibited by monoclonal antibodies directed against IL-2 and IL-2 receptors; this directly demonstrates that an autocrine mechanism is involved in the growth of a tumor T cell. Some normal, activated T cells may also grow through an autocrine stimulation by IL-2. This is suggested by the recent work of Meuer et al. (35) who showed that two human T-cell clones, stimulated by anticonnotypic antibodies producing IL-2 and bearing IL-2 receptors, and that anti-IL-2 and anti-receptor antibodies partially inhibit their proliferation. Nevertheless, it does not necessarily follow that this is a general property of T cells involved in a normal immune response.

IL-2 receptors of normal T cells are expressed only after stimulation by an antigen, a mitogen, or anti-clonotypic antibodies, and their expression is transient and lasts no longer than a few cell divisions (18, 36, 37). The regulation of IL-2 receptor expression may function as a fail-safe mechanism to prevent the uncontrolled growth of T cells. One difference between IARC 301 and the T-cell clones of Meuer et al. (35) is that the IL-2 receptor expression on IARC 301 does not seem to depend upon stimulation. This difference may be critical for IARC 301 permanent growth in vitro, and such a mechanism might be involved in some T-cell tumors. IARC 301 presents a good experimental model to study the intracellular events due to an autocrine stimulation of growth by IL-2. Some of these events probably also play a role in IL-2 stimulation of normal T cells, and an understanding of these pathways should provide insights into the mechanism of regulation of T-cell growth.

We are grateful to Véronique Cornet for her skilful technical help. We are indebted to Dr. Gérard Buttin for his constant support throughout this work. We thank Dr. L. Montagnier and D. Guéant for performing reverse transcriptase assays. DMS1 and DMS3 were kindly provided by Dr. K. Smith, and anti-Tac antibodies, by Dr. W. Greene. This work was supported by the Association pour la Recherche sur le Cancer, the Ligue Nationale Française contre le Cancer, the Fondation pour la Recherche Médicale Française, and the Université Pierre et Marie Curie.