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# The Role of the Multichain IL-2 Receptor Complex in the Control of Normal and Malignant T-Cell Proliferation

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**Antigen-induced activation of resting T-cells induces the synthesis of interleukin-2 (IL-2), as well as the expression of specific cell surface receptors for this lymphokine. There are at least two forms of the cellular receptors for IL-2, one with a very high affinity and the other with a lower affinity. We have identified two IL-2 binding peptides, a 55-kd peptide reactive with the anti-Tac monoclonal antibody, and a novel 75-kd non-Tac IL-2 binding peptide. Cell lines bearing either the p55, Tac, or the p75 peptide alone manifested low-affinity IL-2 binding, whereas cell lines bearing both peptides manifested both high- and low-affinity receptors. Fusion of cell membranes from low-affinity IL-2 binding cells bearing the Tac peptide alone with membranes from a cell line bearing the p75 peptide alone generates hybrid membranes bearing high-affinity receptors. We propose a multichain model for the high-affinity IL-2 receptor in which both the Tac and the p75 IL-2 binding peptides are associated in a receptor complex.**

**In contrast to resting T-cells, human T-cell lymphotropic virus I-associated adult T-cell leukemia cells constitutively express large numbers of IL-2 receptors. Because IL-2 receptors are present on the malignant T-cells but not on normal resting cells, clinical trials have been initiated in which patients with adult T-cell leukemia are being treated with either unmodified or toxin-conjugated forms of anti-Tac monoclonal antibody directed toward this growth factor receptor.**

## Introduction

The human body defends itself against foreign invaders such as bacteria and viruses by a defense system that involves antibodies and thymus-derived lymphocytes (T-cells). The success of this response requires that human T-cells change from a resting to an activated state. Activated T-cells are responsible for the regulation of the immune response, as well as for the elimination of foreign invaders and the rejection of transplanted organs. Failure of the T-cells to become activated and function normally may be associated with serious disease and death. The sequence of events involved in the activation of human T-cells begins when resting T-cells circulating in the bloodstream initially encounter a foreign pathogen. The appropriately processed and presented foreign antigen must interact with a T-cell surface receptor for the specific antigen. This human T-cell antigen receptor has been shown to be a 90-kd polymorphic heterodimer of $\alpha$ and $\beta$ chains, each approximately 40 to 50 kd, associated with three or more 20- to 28-kd nonpolymorphic polypeptide chains identified by the T3 monoclonal antibody. Following the interaction of the antigen presented in the context of products of the major histocompatibility locus and the macrophage-derived interleukin-1 with the antigen receptor, T-cells express the gene encoding the lymphokine IL-2 (*1,2*). To exert its biological effect, IL-2 must interact with specific high-affinity membrane receptors. Resting T-cells do not express IL-2 receptors, but receptors are rapidly expressed on T-cells after activation with an antigen or mitogen (*3,4*). Thus, the growth factor IL-2 and its receptor are absent in resting T-cells, but after activation the genes for both proteins become expressed. A failure of the production of either the growth factor or its receptor results in failure of the T-cell immune response. Although the interaction of appropriately presented antigen with its specific polymorphic receptor complex confers specificity for a given immune response, the interaction of IL-2 with IL-2 receptors determines its magnitude and duration. Furthermore, IL-2 is required for the development of the functional capacities of the T-lymphocyte.

Progress in the analysis of the structure, function, and expression of the human IL-2 receptor was greatly facilitated by our production of the anti-Tac monoclonal antibody that recognizes the human receptor for IL-2 (*5,6*) and blocks the binding of IL-2 to this receptor.

Using quantitative receptor binding studies employing radiolabeled anti-Tac and radiolabeled IL-2, it was shown that activated T-cells and IL-2-dependent T-cell lines express 5- to 20-fold more binding sites for the Tac antibody than for IL-2 (*7,8*). Employing high concen-

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trations of IL-2, Robb et al. (*9*) resolved these differences by demonstrating two affinity classes of IL-2 receptors. On various cell populations, 5 to 15% of the IL-2 receptors had a binding affinity for IL-2 in the range of $10^{-11}$ to $10^{-12}$ M, whereas the remaining receptors bound IL-2 at a much lower affinity, approximately $10^{-8}$ or $10^{-9}$ M. Such low-affinity sites were found whenever high-affinity sites were found, including murine and human T- and B-cells of both normal and leukemic origin. The high-affinity receptors appear to mediate the physiological responses to IL-2, since the magnitude of cell responses is closely correlated with the occupancy of these receptors. As outlined below, we have utilized the anti-Tac monoclonal antibody to: characterize the human receptor for IL-2; molecularly clone cDNAs for the human IL-2 receptor; analyze disorders of IL-2 receptor expression on leukemic cells; and develop protocols for the therapy of patients with IL-2 receptor-expressing adult T-cell leukemia and autoimmune disorders and for individuals receiving organ allografts.

## Chemical Characterization of the IL-2 Receptor

The IL-2 binding receptor peptide identified by the anti-Tac monoclonal on phytohemagglutinin (PHA)-activated normal lymphocytes was shown to be a 55-kd glycoprotein (*6,10*). Leonard and co-workers (*6,10*) defined the post-translational processing of this 55-kd glycoprotein by employing a combination of pulse-chase and tunicamycin experiments. The IL-2 receptor was shown to be composed of a 33-kd peptide precursor following cleavage of the hydrophobic leader sequence. This precursor was cotranslationally *N*-glycosylated to 35- and 37-kd forms. After a 1-hour chase, the 55-kd mature form of the receptor appeared, suggesting that *O*-linked carbohydrate was added to the IL-2 receptor. Furthermore, the IL-2 receptor was shown to be sulfated (*11*) and phosphorylated on a serine residue (*12*).

There was a series of unresolved questions concerning the IL-2 receptor that were difficult to answer when only the 55-kd Tac peptide was considered. These questions include: What is the structural explanation for the great difference in affinity between high- and low-affinity receptors? How, in light of the short cytoplasmic tail of 13 amino acids (see below), are the receptor signals transduced to the nucleus? How do certain Tac-negative cells (e.g., natural killer cells) make nonproliferative responses to IL-2?

To address these questions, we have investigated the possibility that the IL-2 receptor is a complex receptor with multiple peptides in addition to the one identified by anti-Tac. The MLA-144 Gibbon T-cell line binds IL-2, yet does not bind four different antibodies (including anti-Tac and 7G7) that react with the Tac peptide. This cell line manifests 6800 receptors per cell with an affinity of 14 nM (*13*). On the basis of crosslinking studies using [$^{125}$I]IL-2, this IL-2-binding receptor peptide was shown to be larger than the Tac peptide with an approximate $M_r$ of 75,000. When similar crosslinking studies were performed on the cell line MT-1 that manifests only low-affinity receptors, the 55-kd Tac peptide was demonstrated. In contrast, both the 55-kd Tac peptide and the p75 IL-2 binding peptide were expressed on all cell lines (e.g., HUT 102) that manifested both high and low-affinity receptors. Furthermore, fusion of cell membranes from low-affinity IL-2 binding cell lines bearing the Tac peptide alone with membranes from a cell line bearing the p75 peptide alone generated hybrid membranes bearing high-affinity receptors. These studies support our multichain model for the high-affinity IL-2 receptor in which an independently existing Tac or p75 peptide would represent low-affinity receptors, whereas high-affinity receptors would be expressed when both peptides are present and associated in a receptor complex (*13*).

## Molecular Cloning of cDNAs for the Human 55-kd Tac IL-2 Receptor Peptide

Three groups (*14–16*) have succeeded in cloning cDNAs for the IL-2 receptor protein. The deduced amino acid sequence of the IL-2 receptor indicates that this peptide is composed of 251 amino acids, as well as a 21-amino acid signal peptide. The receptor contains two potential *N*-linked glycosylation sites and multiple, possible *O*-linked carbohydrate sites. Finally, there is a single hydrophobic membrane region of 19 amino acids and a very short (13 amino acid) cytoplasmic domain. Potential phosphate acceptor sites (serine and threonine, but not tyrosine) are present within the intracytoplasmic domain. However, the cytoplasmic domain of the IL-2 receptor peptide identified by anti-Tac appears to be too small for enzymatic function. Thus, this receptor differs from other known growth factor receptors that have large intracytoplasmic domains with tyrosine kinase activity. The p75 peptide associated with the Tac peptide may play a critical role in the transduction of the IL-2 signal to the nucleus. Leonard and co-workers (*17*) have demonstrated that the single gene encoding the IL-2 receptor consists of eight exons on chromosome 10p14. However, mRNAs of two different sizes (approximately 1500 and 3500 bases long) have been identified. These classes of mRNA differ because of the utilization of two or more polyadenylation signals (*14*). Receptor gene transcription is initiated at two principal sites in normal activated T-lymphocytes (*17*). Furthermore, sequence analyses of the cloned DNAs also indicate that alternative mRNA splicing may delete a 216-base pair segment in the center of the protein coding sequence encoded by the fourth exon (*14,17*). Using expression studies of cDNAs in COS-1 cells, Leonard and co-workers (*14*) demonstrated that the unspliced, but not the spliced form, of the mRNA was translated into the cell surface receptor that binds IL-2 and the anti-Tac monoclonal antibody.

## Distribution of IL-2 Receptors

As discussed above, the majority of resting T-cells, B-cells, or macrophages in the circulation do not display IL-2 receptors. Specifically, less than 5% of freshly isolated, unstimulated human peripheral blood T-lymphocytes react with the anti-Tac monoclonal antibody. The majority of T-lymphocytes, however, can be induced to express IL-2 receptors by interaction with lectins, monoclonal antibodies to the T-cell antigen receptor complex, or alloantigen stimulation. Furthermore, IL-2 receptors have also been demonstrated on activated B-lymphocytes (*18*) and activated monocytes.

Rubin et al. (*19*) have demonstrated that, in addition to cellular IL-2 receptors, activated normal peripheral blood mononuclear cells and certain lines of T- and B-cell origin release a soluble form of the IL-2 receptor into the culture medium. Using an enzyme-linked immunosorbent assay, which employs two monoclonal antibodies that recognize distinct epitopes on the human IL-2 receptor, it was shown that normal individuals have measurable amounts of IL-2 receptors in their plasma and that certain lymphoreticular malignancies are associated with elevated plasma levels of this receptor. The release of soluble IL-2 receptors appears to be a consequence of cellular activation of a variety of cell types that may play a role in the regulation of the immune response. Furthermore, the analysis of plasma levels of IL-2 receptors may provide an important new approach to the analysis of lymphocyte activation *in vivo*.

## Lymphocyte Functions That Are Regulated by the Interaction of IL-2 with Its Receptor

The anti-Tac monoclonal antibody has been used to define those lymphocyte functions that require an interaction of IL-2 with its inducible receptor on activated T- and B-lymphocytes. The addition of anti-Tac to cultures of human peripheral blood mononuclear cells inhibited a variety of immune reactions. Anti-Tac profoundly inhibited the proliferation of T-lymphocytes stimulated by soluble antigens and by cell surface antigens (autologous and allogeneic mixed lymphocyte reactions). Upon activation, human T-cells acquire surface structures, which in large measure are growth factor receptors not easily detectable during their resting stage (*20,21*). The addition of anti-Tac at the initiation of cultures of T-cells stimulated by mitogens, antigens, or the T3 antibody inhibited the expression of the late-appearing activation antigens examined, the insulin and transferrin receptors, and Ia antigens (*20,21*). Anti-Tac was also shown to inhibit a series of T-cell functions, including the generation of both cytotoxic and suppressor T-lymphocytes in allogeneic cell cultures, but anti-Tac did not inhibit their action once generated. In contrast to the action on T-cells, anti-Tac did not inhibit the activation of natural killer cells by IL-2. In general, such cells are Tac-antigen negative but express the p75 binding peptide (Tsudo and Waldmann, unpublished observations).

## Disorders of IL-2 Expression in Adult T-Cell Leukemia

A distinct form of mature T-cell leukemia was defined by Takasuki and co-workers (*22*) and termed adult T-cell leukemia (ATL). ATL is a malignant proliferation of mature T-cells that have a propensity to infiltrate the skin. Cases of ATL are associated with hypercalcemia and usually have a very aggressive course. The ATL cases are clustered within families and geographically, occurring in the southwest of Japan, the Caribbean basin, and in certain areas of Africa. HTLV-I has been shown to be a primary etiologic agent in ATL (*23*). All the populations of leukemic cells we have examined from patients with HTLV-I-associated ATL expressed the Tac antigen (*24*). The expression of IL-2 receptors on ATL cells differs from that of normal T-cells. First, unlike normal T-cells, ATL cells do not require prior activation to express IL-2 receptors. Furthermore, using a $^{3}$H-labeled anti-Tac receptor assay, HTLV-I-infected luekemic T-cell lines characteristically expressed 5- to 10-fold more receptors per cell (270,000–1,000,000) than did maximally PHA-stimulated T-lymphoblasts (30,000–60,000). In addition, whereas normal human T-lymphocytes maintained in culture with IL-2 demonstrate a rapid decline in receptor number, adult ATL lines do not show a similar decline. It is conceivable that the constant presence of high numbers of IL-2 receptors on ATL cells and/or the aberrancy of these receptors may play a role in the pathogenesis of uncontrolled growth of these malignant T-cells.

As noted above, T-cell leukemias caused by HTLV-I, as well as all T-cell and B-cell lines infected with HTLV-I, universally express large numbers of IL-2 receptors. An analysis of this virus and its protein products suggests a potential mechanism for this association between HTLV-I and IL-2 receptor expression. The complete sequence of HTLV-I has been determined by Seiki and colleagues (*25*). In addition to the presence of typical long terminal repeats (LTRs), *gag*, *pol*, and *env* genes, retroviral gene sequences common to other groups of retroviruses, HTLV-I and -II were shown to contain an additional genomic region between *env* and the 3′ LTR referred to as pX or more recently as *tat*. Sodroski and colleagues (*26*) demonstrated that this pX or *tat* region encodes a 42-kd protein, now termed the *tat* protein, that is essential for viral replication. The mRNA for this protein is produced by a double splicing event. These authors demonstrated that the *tat* protein acts on a receptor region within the LTR of HTLV-I, stimulating transcription. This *tat* protein may also play a central role in directly or indirectly increasing the transcription of host genes such as the IL-2 receptor gene involved in T-cell activation and HTLV-I-mediated T-cell leukemogenesis.

## The IL-2 Receptor as a Target for Therapy in Patients with ATL and Patients with Autoimmune Disorders and Individuals Receiving Organ Allografts

The observation that ATL cells constitutively express large numbers of IL-2 receptors identified by the anti-Tac monoclonal antibody, whereas normal resting cells and their precursors do not, provides the scientific basis for therapeutic trials using agents to eliminate the IL-2 receptor-expressing cells. Such agents could theoretically eliminate Tac-expressing leukemic cells or activated T-cells involved in other disease states while retaining the mature, normal T-cells and their precursors that express the full repertoire for T-cell immune responses. The agents that have been used or are being prepared include unmodified anti-Tac monoclonal; toxin (e.g., the A chain of ricin toxin, Pseudomonas toxin) conjugates of anti-Tac; and conjugates of alpha-emitting isotopes (e.g., bismuth-212) with anti-Tac.

We have initiated a clinical trial to evaluate the efficacy of administered IV anti-Tac monoclonal antibody in the treatment of patients with ATL (*27*). None of the seven patients treated suffered any untoward reactions and none produced antibodies to the mouse immunoglobulin or to the idiotype of the anti-Tac monoclonal. Two of the patients had a temporary partial response or complete remission following anti-Tac therapy. In one of these patients, therapy was followed by a 5-month remission, as assessed by routine hematological tests, immunofluorescence analysis of circulating T-cells, and molecular genetic analysis of arrangement of the genes encoding the β chain of the T-cell antigen receptor. Following the 5-month remission, the patient's disease relapsed, but a new course of anti-Tac infusions was followed by a virtual disappearance of skin lesions and an over 80% reduction in the number of circulating leukemic cells. Two months subsequently, leukemic cells were again demonstrable in the circulation. At this time, although the leukemic cells remained Tac positive and bound anti-Tac *in vivo*, the leukemia was no longer responsive to infusions of anti-Tac and the patient required chemotherapy. This patient may have had the smouldering form of ATL, wherein the leukemic T-cells may still require IL-2 for their proliferation. Alternatively, the clinical responses may have been mediated by host cytotoxic cells reacting with the tumor cells bearing the anti-Tac mouse immunoglobulin on their surface by such mechanisms as antibody-dependent cellular cytotoxicity.

These therapeutic studies have been extended *in vitro* by examining the efficacy of toxins coupled to anti-Tac to selectively inhibit protein synthesis and viability of Tac-positive ATL lines. The addition of anti-Tac antibody coupled to the A chain of the toxin ricin effectively inhibited protein synthesis by the HTLV-I-associated, Tac-positive ATL line HUT 102-B2 (*28*). In parallel studies performed in collaboration with FitzGerald et al. (*29*), Pseudomonas exotoxin conjugates of anti-Tac inhibited protein synthesis by Tac-expressing HUT 102-B2 cells, but not that by the Tac-negative acute T-cell line MOLT-4, which does not express the Tac antigen.

The action of toxin conjugates of monoclonal antibodies depends on their ability to be internalized by the cell and released into the cytoplasm. Anti-Tac bound to IL-2 receptors on leukemic cells is internalized slowly into coated pits and then endosomic vesicles. Furthermore, the toxin conjugate does not pass easily from the endosome to the cytosol, as required for its action on elongation factor 2. To circumvent these limitations, an alternative cytotoxic reagent was developed that could be conjugated to anti-Tac and that was effective when bound to the surface of leukemic cells. It was shown that bismuth-212 ($^{212}$Bi), an alpha-emitting radionuclide conjugated to anti-Tac by use of a bifunctional chelate, was well suited for this role (*30*). Activity levels of 0.5 μCi or the equivalent of 12 rad/mL of alpha radiation targeted by $^{212}$Bi-anti-Tac eliminated greater than 98% of the proliferative capacity of the HUT 102-B2 cells, with only a modest effect on IL-2 receptor-negative lines. This specific cytotoxicity as blocked by excess unlabeled anti-Tac, but not by human IgG. Thus, $^{212}$Bi-anti-Tac is a potentially effective and specific immunocytotoxic agent for the elimination of IL-2 receptor-positive cells.

In addition to its use in the therapy of patients with ATL, antibodies to the IL-2 receptors are being evaluated as potential therapeutic agents to eliminate activated IL-2 receptor-expressing T-cells in other clinical states, including certain autoimmune disorders and in protocols involving organ allografts. The rationale for the use of anti-Tac in patients with the disease aplastic anemia is derived from the work of Zoumbos and co-workers (*31*) who have demonstrated that select patients with aplastic anemia have increased numbers of circulating Tac-positive cells. In this group of patients, the Tac-positive, but not Tac-negative, T-cells were shown to inhibit hematopoiesis when cocultured with normal bone marrow cells. Furthermore, we have demonstrated that anti-Tac inhibits the generation of activated suppressor T-cells (Oh-ishi and Waldmann, unpublished observations). Studies have been initiated to define the value of anti-Tac in the therapy of patients with aplastic anemia. The rationale for the use of an antibody to IL-2 receptors in recipients of renal and cardiac allografts is that anti-Tac inhibits the proliferation of T-cells to foreign histocompatibility antigens expressed on the donor organs and prevents the generation of cytotoxic T-cells in allogeneic cell cocultures. Furthermore, in studies by Strom and co-workers (*32*), the survival of renal and cardiac allografts was prolonged in rodent recipients treated with an anti-IL-2 receptor monoclonal antibody. Thus, the development of monoclonal antibodies directed toward the IL-2 receptor expressed on ATL cells, on autoreactive T-cells of certain patients with autoimmune disorders, and on host T-cells responding to foreign histocompatibility an-

tigens on organ allografts may permit the development of rational new therapeutic approaches in these clinical conditions.

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