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THE IL-2 RECEPTOR: ONE MYSTERY SOLVED

VALLEY FORGE, PA—If you can't learn from history, what can you learn from? Mystery.

And one mystery, that in recent months has provoked a particularly instructive solution, is why the interleukin-2 (IL-2) receptor binds its ligand with two widely different affinities. Speaking at this year's Smith Kline & French Laboratories Research Symposium, Richard Robb (E. I. du Pont de Nemours & Co., Glenholden, PA) described his own contributions to answering this elusive question, as well as experiments aimed at correlating ligand binding with receptor subunit structure.

Researchers have known for several years that activated T cells bind IL-2 with avidities that differ as much as 5,000-fold. Subsequent to cloning the gene for the low-affinity protein (Tac), anti-Tac antibodies were shown to block IL-2 interaction with *both* affinity states. Workers therefore postulated that the 55 kD Tac protein interacted with a second subunit to form the high-affinity receptor.

The breakthrough in understanding the nature of the second subunit, Robb said, came as a result of experiments utilizing the natural killer (NK) lymphocyte cell line, YT. These cells show an intermediate IL-2 binding-affinity, and significantly the binding is not inhibited by anti-Tac antibodies. It is, however, associated with a new 70–75 kD glycoprotein that Robb has designated β. When YT cells are stimulated with interleukin-1 (IL-1), they show a precipitous decrease in the number of β-type binding sites and a corresponding increase in the number of sites that bind IL-2 with high affinity. The implication is that the intermediate sites are associating with Tac protein synthesized as a result of the IL-1 treatment. A monoclonal antibody directed against the β-subunit binding domain of IL-2 provided the proof.

Robb showed that antibodies specific for epitopes at the N-terminal portion of IL-2 prevent this lymphokine from binding to β-subunits on YT cells and to high-affinity sites on stimulated cells. The antibodies do not, however, affect binding to cell lines that only express Tac. Studies of IL-2 receptor crosslinking confirmed the high-affinity form of receptor is indeed a heterodimer composed of one β-subunit and one Tac chain.

Thus there are at least three forms of IL-2 receptor with different cellular distributions and activities. One form is composed of the Tac protein, either as a single chain or a ligand-crosslinked homodimer. It is abundant on activated lymphocytes, binds IL-2 with a low affinity, does not internalize ligand, and is not definitively correlated with any known cellular response. A second form is composed of the β-chain. It appears to be present in small numbers on a variety of cells, including resting T cells, large granular lymphocytes, and certain B-cell lines. These molecules bind IL-2 with an intermediate affinity, internalize ligand, and mediate such cellular responses as short-term NK activation and induction of Tac biosynthesis. A third form is a ternary complex composed of a Tac and β-chain crosslinked by IL-2. It is characterized by a high-affinity ligand binding and correlates well with the proliferative response of activated T, B, and NK cells.

In regard to the role of individual Tac molecules, Robb noted their abundance on activated lymphocytes, and that a soluble form, which is quite stable, is released from such cells. He suggested this soluble Tac removes IL-2 from the circulation and thus modulates the IL-2 response.

Concerning the correlation of ligand binding and the structure of the individual receptor subunits, Robb showed that IL-2 can be chemically crosslinked to one or more lysine residues encoded by exons 2 and 3 of the Tac gene. However, deletion analysis of Tac cDNA demonstrated that an active receptor configuration is also critically dependent on structural features encoded by exon 4. Though it is unlikely that these types of studies will localize a single site sufficient for IL-2 binding, they will assist in interpreting data derived from crystallographic analyses. Thus they provide a first step toward the design of molecular mimics and antagonists of this potent and versatile lymphokine.

IL-2 and Human Retroviruses

Warner Greene (Duke University School of Medicine, Durham, NC), who collaborated with Robb on many of these studies, added another dimension to the IL-2 story when he described recent work with Robert Gallo and Flossie Wong-Staal of the National Cancer Institute.

Infection of T4 lymphocytes with the HTLV-I retrovirus can lead to the aggressive and often fatal neoplasm, Adult T Cell Leukemia. Such transformed cells characteristically express abnormally large numbers of Tac receptors. To determine if this overexpression might be due to virally encoded functions, Greene and his co-workers transfected cells with plasmids containing a chloramphenicol acyltransferase (*cat*) reporter gene linked to promoter elements of the Tac or IL-2 genes. Induction of HTLV-I transactivating (*tat*) protein in these transformants positively regulated *cat* transcription from either promoter, suggesting that HTLV-I-induced transformation involves uncontrolled autocrine T cell growth.

Related experiments using the AIDS virus (HIV) demonstrated that infection of peripheral T4 lymphocytes or Jurkat T cells all but eliminates mitogen-induced IL-2 gene expression, but does not affect expression of the Tac receptor gene. Perhaps these results provide a clue to the solution of another mystery: How *does* HIV kill infected helper lymphocytes? **—Harvey Bialy**

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