MEETING REPORT

WHAT DO T-CELL RECEPTORS RECEIVE?

DANBURY, Conn.—How does the T-cell receptor recognize antigens on the surface of cells? What is the nature of the antigen that binds to it? These were two of the issues addressed at the Boehringer-Ingelheim Centennial Symposium,"Frontiers in Molecular Immunology," held here August 15–16.

Mark Davis (Stanford University) has been studying the ways in which T-cell receptor genes are rearranged to generate the large repertoire of antigen binding sites on the surfaces of T lymphocytes. Although there are many similarities between the genetic structures of immunoglobulins and T-cell receptors, Davis described a number of differences that may bear on a key question: How does the T-cell receptor recognize foreign antigens only in the context of a major histocompatibility complex (MHC) determinant. At the gene-level, the variable sequences of the receptor differ much more from one another than do the hypervariable and variable regions of immunoglobulins. The receptor's variable sequences also appear to have additional regions of hypervariability. Three of these are relatively close to one another on the outside of a typical immunoglobulin structure. Davis postulates that they might constitute the site of interaction of the T-cell receptor and antigen-MHC determinants.

In order to prepare sufficient quantitities of receptor to test this hypothesis by ligand binding studies and other functional assays, Davis has been using rDNA techniques to insert T-cell receptor genes into a cloned immunoglobulin. He thus uses the immunoglobulin as an "expression casette" for the production of hybrid molecules with T-cell receptor regions contained within immunoglobulin frameworks. Davis reported he has used such an expression casette to produce large quantities of human growth hormone.

Emil Unanue (Washington University School of Medicine, St. Louis, MO) presented an elegant series of experiments that bear on the other aspect of the question: What is the nature of the antigen recognized by the T-cell receptor? In one experiment, he allowed macrophages to ingest hen egg lysozyme (HEL), and thirty minutes later gently fixed the cells. He found that the macrophages can indeed bind T cells expressing HEL receptors. When the order of steps was reversed (the macrophages fixed, and then given the enzyme) no binding occured. In a third variation, he predigested the HEL and then presented the fragments to fixed cells. In this case, he found that a particular fragment (residues 52–61) is sufficient for T-cell binding. Thus the nature of antigen processing would appear to be proteolytic digestion in the interior of the macrophage, followed by delivery of the processed antigen to the cell surface.

The recognition is exquisitely specific: the autologous mouse peptide, which does not stimulate binding, differs by only a single amino acid (at position 56) from the HEL fragment. The experiments also point out an important difference between epitopes recognized by immunoglobulins and those seen by T cells. B cells make antibodies to conformationally determined aspects of antigenic proteins which are present on exposed surfaces. T cells, on the other hand, appear to respond to areas of the protein that are normally inaccessible (hence the need for antigen processing). The HEL fragment identified, for example, is hidden in the interior of the lysozyme molecule.

—Harvey Bialy

Barry Bloom

EIGHT CHALLENGES TO IMMUNOLOGY

In the summary talk at the Boehringer-Ingelheim Centennial Symposium, Barry Bloom (Albert Einstein College of Medicine, New York) posed what he called the important unanswered questions confronting scientists in their attempts to modulate the immune response. According to Bloom, the perennial problems of immunology are:

- What are the mechanisms by which tolerance is induced and maintained (self vs. non-self discrimination)?
- What is the biological significance of major histocompatibility complex (MHC) restriction?
- What are the relative contributions of junctional and somatic events in generating B- and T-cell diversity?
- How are immunoglobulin subclasses regulated, and what are their individual functions?
- How are signals from the interaction of receptors with antigen, growth factors, and other effector molecules transduced so as to exert their regulatory effects on cells?
- Is there immune surveillance of tumors?
- What are the mechanisms of adjuvant action, and can we develop new adjuvants?
- What do immunoregulatory genes really regulate, and how important are they in man?

He closed by posing a major challenge: "There are millions of people for whom the existing tools for immunization are either unavailable or beyond their reach. There is renewed hope for simple, inexpensive and long acting recombinant vaccines based on vaccinia, adenovirus, and possibly mycobacteria, that could have an enormous impact on the quality of life in the Third World. And that hope can only be addressed by scientists in the more developed countries."

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