Histocompatibility Restriction Explained

Research is revealing the molecular basis of histocompatibility restriction and perhaps the way in which the immune system discriminates between self and nonself

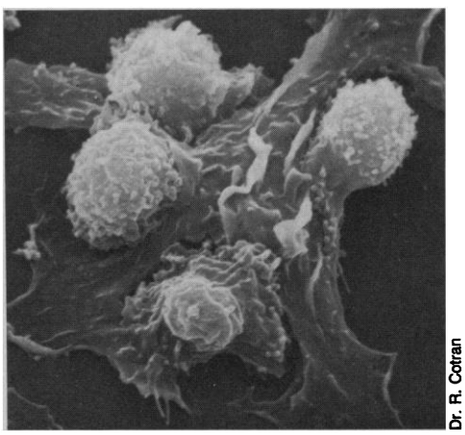
DISCOVERIES within the past year or so are helping to clear up at least one, and possibly two, of the unsolved mysteries of immunology. The research, some of which is described in a paper beginning on page 865 of this issue of *Science*, is at last uncovering the nature of the histocompatibility antigens' contributions to immune responses.

In addition, the *Science* paper, which comes from Malcolm L. Gefter of the Massachusetts Institute of Technology, Howard M. Grey of the National Jewish Center for Immunology and Respiratory Medicine in Denver, John Smith of Massachusetts General Hospital and Harvard Medical School, and their colleagues, proposes a new hypothesis to account for how the immune system distinguishes between molecules and cells that belong in the body and those that are foreign and should be attacked. The findings have implications for the design of vaccines for enhancing immunity and also of strategies for suppressing it, which may be desirable for fighting organ transplant rejection or autoimmunity.

Although the histocompatibility antigens were originally discovered nearly 50 years ago as the cell surface proteins that trigger the rejection of transplanted tissue by the recipient's immune system, immunologists learned in the 1970s that the proteins play an essential role in all immune responses involving T lymphocytes. Until now the molecular nature of that role has remained both obscure and a subject of some dispute, particularly with regard to the phenomenon called "histocompatibility restriction."

The T lymphocytes, especially those of the helper type, play a key role in the initiation of many immune responses. Helper T cells are activated by an interaction with antigen-presenting cells that display foreign antigens on their surfaces. The helpers in turn stimulate other immune cells, including the antibody-producing B lymphocytes and the killer T cells that destroy cells perceived as foreign, such as virus-infected cells.

In the 1970s, immunologists discovered that helper cells do not recognize foreign antigens by themselves, but only in conjunction with the histocompatibility proteins of the presenting cells. Killer T cells also detect foreign antigens in conjunction with the histocompatibility proteins on the target cells. Restriction means that for a T cell to be activated, its receptor has to recognize a foreign antigen in the context of a particular histocompatibility protein, usually the same one carried by the T cell itself.



Dr. R. Cotran

Restriction in action: *A large, flat macrophage to which four T lymphocytes have attached. The macrophage has engulfed* Listeria monocytogenes *and the T cells are* Listeria*-specific.*

Over the years, there has been a great deal of contention about how a T cell receptor does this—whether it detects the foreign antigen and histocompatibility molecule separately or whether it recognizes them as a single combined entity. The current results, in accord with the findings of other recent immunological research, definitely come down on the side of recognition of a single combined entity. Researchers are finding that a histocompatibility molecule behaves much like a receptor that has a single binding site for peptides derived from foreign antigens. This means that a T cell recognizes a foreign peptide after it has bound to an appropriate histocompatibility protein.

A variety of developments have led up to this current understanding. For one, researchers in a number of laboratories, including Grey's and that of Emil Unanue at Washington University School of Medicine in St. Louis, showed that antigenic proteins are not presented to helper T cells as intact molecules, but are apparently first broken down to peptides in the presenting cell. Usually only a few of the peptides that might be released by protein breakdown are immunogenic, that is, capable of stimulating T cells and initiating an immune response.

Next came direct demonstrations, first by the Unanue group and then by Grey and his colleagues, that immunogenic peptides bind directly to histocompatibility proteins. The histocompatibility proteins are encoded by a large multigene complex, called the major histocompatibility complex. Each of the several genes in the complex has as many as 50 to 100 variants. The histocompatibility proteins encoded by these variant genes differ in their abilities to present antigens and initiate immune responses. These differences among histocompatibility proteins had been postulated to be caused by the varying abilities of the molecules to bind and present antigens, although there was no direct proof of this until the current work.

Unanue and his colleagues and Gefter, Grey, and theirs have found that there is a correlation between the ability of a histocompatibility protein to bind a particular immunogenic peptide and its ability to generate an immune response by helper T cells in collaboration with that peptide. "The binding has an immunologically relevant effect," Unanue explains. "It determines whether there will be a response or not."

In addition, the results of Gefter, Grey, and Smith show that a histocompatibility protein has only one peptide binding site. "You can think of a histocompatibility protein as a cell surface receptor," Gefter says. "It can bind various types of peptides at the same site."

This result was unexpected. "People thought that histocompatibility proteins would have many binding sites," notes Ronald Schwartz of the National Institute of Allergy and Infectious Diseases. Foreign antigens vastly outnumber even the histocompatibility protein population, a situation that would necessitate having each histocompatibility protein bind many, apparently different peptides. Such a situation would be unusual in cell biology, because ordinary receptors bind just a limited number of structurally similar molecules.

Kinetic analysis by Grey and his colleagues of the binding of immunogenic peptides by histocompatibility antigens also points to the unusual nature of the interaction. "Our data suggest that the interaction is quite slow, but is quite stable once it occurs," Grey says. Tania Watts and Harden McConnell of Stanford University have obtained similar results. These findings indi-

cate that the three-dimensional structure of the peptide or histocompatibility protein must change for the binding to occur—as would probably be necessary for a histocompatibility molecule to bind many different peptides at the same site.

An explanation of histocompatibility restriction has to include ways to account both for the binding of different peptides by a single histocompatibility molecule and for the activation of unique T cells specific for each antigen. Unanue and Gefter, Grey, and Smith suggest that immunogenic peptides consist of amino acids that form the histocompatibility contacts, intermingled with amino acids that interact with the T cell receptors. For example, Gefter and his colleagues find that immunogenic peptides that are presented by the same histocompatibility molecule display a common structural motif. They contain identical or at least similar amino acids at corresponding sites, even though the proteins from which the peptides came are not obviously related.

Some of these common amino acids, which do not have to be next to one another in the linear peptide sequence, presumably form the contacts with the histocompatibility protein, whereas other of the amino acids, which vary from one peptide to the next, are the ones recognized by T cells specific for a particular antigen. The Gefter group has also found that one peptide could be made to act like another in T cell activation, if two of the amino acids of the first peptide were replaced by the two corresponding amino acids of the second. This clearly shows that immunogenic peptides contain amino acid residues that can be recognized by specific T cells.

The work of the Gefter and Unanue groups has all been done with the class II histocompatibility proteins that participate in interactions involving helper T cells. The class I histocompatibility proteins are the restricting elements for interactions between killer T cells and their targets, and it will be interesting to see if the class I molecules work in the same way as those of class II. The indications are that they might. For example, Alain Townsend of the John Radcliffe Hospital in Oxford, England, and his colleagues have evidence that killer cells recognize class I histocompatibility proteins in conjunction with peptides released from viral proteins in the target cells.

In the course of their investigations, Gefter, Grey, and their colleagues made an observation that appears to be completely at odds with the hypothesis that peptide binding to a histocompatibility protein goes hand-in-hand with presentation to a T cell. They found that one peptide, from a protein made by the bacterial virus called bacteriophage λ, binds very tightly to a histocompatibility protein, but that the combination is ineffective in antigen presentation and T cell activation. The peptide is capable of stimulating an immune response in combination with another histocompatibility protein, however, even though it is bound less avidly by the active protein than the inactive one.

The failure to respond in the one case appears to be the result of a lack of T cells that can recognize the λ peptide in conjunction with that particular histocompatibility protein. If so, this would mean, among other things, that peptide binding to a histocompatibility antigen is not sufficient for generating an immune response, although it is necessary. Moreover, according to Gefter, the "hole" in the T cell repertoire may be a reflection of immunological tolerance, in which the immune system learns not to attack molecules that belong in the body.

"You can think of a histocompatibility protein as a cell surface receptor."

The Gefter group made another surprising observation when they compared the amino acid sequences of immunogenic peptides to those of the histocompatibility proteins to which the peptides bind. The investigators found that the common structural motif of the immunogenic peptides is also present in a segment of the corresponding histocompatibility protein. "You wouldn't expect that for random proteins from nature," Gefter points out.

On the basis of these findings, he proposes that a histocompatibility molecule contains, in addition to the receptor site for immunogenic peptides, another domain that is complementary in structure to the receptor site and capable of binding to it. The complementary domain would in effect be an internal ligand for the receptor. According to this model, the structures of immunogenic peptides would have to resemble the internal ligand on a histocompatibility protein to bind to the receptor.

But too much similarity may make a peptide invisible to the T cell repertoire. The λ peptide has even more amino acids in common with the histocompatibility protein to which it binds tightly without stimulating an immune response than with the other protein with which it does trigger a response. Consequently, when the peptide binds to the receptor on the inactive histocompatibility protein, Gefter suggests, the combination looks so much like the original histocompatibility molecule that it cannot be detected as foreign.

The overall idea is that a peptide has to resemble the internal ligand of a histocompatibility protein to be immunogenic, but if the resemblance is too great, the peptide will be confused with a self molecule and will be tolerated by the immune system. "This reduces the enormous complexity of how the immune system knows what is self and what is nonself to the inspection of a few amino acids in a peptide," Gefter says.

More work will be needed to confirm this model for self, nonself discrimination by the immune system. Both Schwartz and Grey point to a possible weakness in the hypothesis. The binding of a foreign peptide to a histocompatibility protein would seem to be difficult to achieve if the peptide must first displace another portion of the protein itself from the receptor site. Grey notes, however, that the model fits the data thus far.

Moreover, Gefter says that such displacement may not be necessary. He suggests that the interaction between the receptor and internal ligand portions of a histocompatibility protein may be temporary in nature, perhaps occurring just briefly after the protein is synthesized. By the time the protein is ready for combination with a foreign peptide, it may have already opened up to allow the binding.

Additional comparisons of the structures of immunogenic peptides with the histocompatibility proteins that present them could help to strengthen or weaken the hypothesis. So could a knowledge of the three-dimensional structures of histocompatibility proteins both alone and in combination with antigen, which can be obtained from the x-ray crystallographic studies now under way in at least two laboratories. Gefter's model can also be tested by synthesizing peptides that either should or should not act as immunogens with particular histocompatibility molecules and determining whether the peptides behave as predicted.

Even if the immune system does not distinguish between foreign and self molecules as proposed by the Gefter group, the identification of histocompatibility molecules as receptors for immunogenic peptides has potential clinical applications. For example, effective vaccines might be made by designing peptides that bind to the receptors to produce combinations that are effective T cell activators. Conversely, it should also be possible to design peptides that bind to and block the histocompatibility receptors without activating immune responses. Such peptides might prove useful as immune suppressants that could be used to fight transplant rejection or autoimmune diseases. ■ JEAN L. MARX