Immunology: Role of Immune Response Genes

The discovery in the mid-1960's that specific genes determine whether an animal can make immune responses to certain antigens was, for several reasons, something of a surprise to immunologists. It was surprising because the immune response (Ir) genes did not code for antibody structure; because the number of genes necessary to achieve the known specificity of immune responses seemed prohibitively high; and because most immunologists accepted the clonal selection theory as an explanation of how immune responses are triggered.

Now, although not all of the questions about how Ir genes work have been answered, investigators are clarifying some aspects of the mechanism of action of the genes, and at the same time, illuminating two of the major unsolved problems of immunology. These are the elucidation of how cells of the immune system interact with one another and the identification of the hitherto elusive receptors for antigen on T (for thymus-derived) lymphocytes. It appears that the Ir gene products may either serve as the receptors or be involved in the cellular interactions, or both.

The first Ir gene identified was one determining the response of guinea pigs to a polypeptide composed only of lysine residues. (The antigens most commonly used for experiments on Ir genes are synthetic polypeptides of limited structural diversity.) Baruj Benacerraf, now at Harvard Medical School, found that strain 2 guinea pigs carry a gene that enables them to mount an immune response against this antigen whereas strain 13 guinea pigs do not. The reverse is true for a gene controlling responses to a polypeptide of glutamic acid and tyrosine residues.

Since these early studies, investigators including Benacerraf and Hugh McDevitt of Stanford University Medical School have identified at least 30 Ir genes in the mouse, guinea pig, rat, rhesus monkey, and probably man. The genes are dominant, and they determine both cellular and humoral immune responses.

McDevitt showed that the Ir gene controlling the response to (T,G)-A--L, a branched synthetic polypeptide that is composed of tyrosine, glutamic acid, alanine, and lysine residues, is genetically linked to a particular histocompatibility antigen whose gene is located in the major histocompatibility complex (MHC) of the mouse. Many Ir genes are now known to be linked with histocompatibility antigens, although there is an additional class of the genes that are not. The latter are not discussed in this article.

Histocompatibility antigens are located on the surfaces of cells; their normal functions are largely unknown but it is known that these are the antigens that elicit rejection of transplanted organs. Genetic linkage means that genes, such as the Ir genes and those for histocompatibility antigens, are usually transmitted together from parent to progeny. And this means that both types of genes are located close together on the same chromosome.

By using standard genetic techniques, researchers have prepared a detailed map of the MHC on chromosome 17 of the mouse. They found that the Ir genes are located within this gene complex in a region called the I region. The total number of Ir genes is unknown but the chromosomal segment containing them is long enough to carry as many as several hundred genes.

Another important observation is that all the responses specified by Ir genes involve the activities of T lymphocytes. There are two major classes of lymphocytes participating in immune responses. The B (for bone marrow–derived) cells are the precursors of the antibody-secreting cells and are thus responsible for humoral immunity. The T cells are the effectors of cellular immunity and may act directly to destroy foreign antigens, including transplanted organs. In addition, they may regulate antibody production by either helping or suppressing B cell activities. Production of antibodies against some antigens does not require the cooperation of helper T cells but production of antibodies against others does. Only the latter is affected by Ir genes.

The finding that Ir genes are involved only in immune responses that depend on the activities of T lymphocytes suggested that the gene products might themselves serve as receptors for antigens on T cells. Most immunologists think that the clonal selection theory applies to both T and B lymphocytes. According to this theory, an immune response is initiated when an antigen combines with a specific receptor for it on the responding lymphocyte. This causes the lymphocyte to divide to produce large numbers of identical cells that perform a particular function, such as secretion of one—and only one—kind of antibody.

The antigen receptors on B cells are immunoglobulin (antibody) molecules. However, the identity of those on T cells is in dispute. Some investigators say that T cells also have receptors consisting of immunoglobulins. Others say that they can find no evidence for the presence of immunoglobulins on T cell surfaces.

Consequently, a great deal of effort has been directed to determining whether the Ir gene products are the T cell receptors. Of equal importance is the question of whether the products participate in the numerous cellular interactions needed to produce immune responses. These include the interactions between T and B cells, between different kinds of T cells, and between T cells and macrophages. (Macrophages are cells that engulf and consume foreign matter; they are also involved in the initiation of T cell activities.)

Several lines of evidence indicate that the Ir gene products are important in controlling interactions between cells of the immune system. The experiments are too complicated to describe here, but Benacerraf and David Katz, also of Harvard Medical School, showed that the T and B lymphocytes of mice cannot cooperate unless they both carry identical genes located in the MHC, and specifically in that portion of the MHC containing the Ir genes. The investigators proposed that genes in the I region code for T cell products needed for interaction with B cells, and also code for the corresponding sites on the B cell membrane. Genes needed for the interaction of T cells and macrophages are also located in the histocompatibility gene complex, according to Ethan Shevach and Alan Rosenthal of the National Institute of Allergy and Infectious Diseases (NIAID).

In a parallel line of experiments, investigators such as Tomio Tada of Chiba University in Japan and Alan Munro and Michael Taussig of Cambridge University in England have been clarifying the manner in which T cells influence B cell activity. Tada has identified a factor produced by T cells that suppresses antibody production by B cells, and the Cambridge investigators have identified a factor that enhances it. Despite the fact that they have opposite effects, the two factors have a number of properties in common. Both are specific in that they are prepared from T cells sensitized to a particular antigen [the dinitrophenyl group complexed with keyhole limpet hemocyanin for the Tada factor, and (T,G)-A--L for the factor studied by Munro and Taussig] and affect production of antibodies only against that antigen. Both factors are proteins with molecular weights of about 50,000.

It is extremely unlikely that the factors are themselves immunoglobulins. Their molecular weights are too low and they do not react with antiserums against immunoglobulins. It does appear, however, that the factors are products of genes in the I region of the MHC of the mouse since they

do react with antiserums against products of that region.

The antiserums used for these experiments are actually directed against Ia (for I region–associated) antigens. Several investigators, including Donald Shreffler at the University of Michigan and Jan Klein, now at the University of Texas Southwestern Medical School, discovered these antigens, which are a group of cell surface proteins whose expression is regulated by genes mapping in the same chromosomal region as the Ir genes. It is not known whether the Ia and Ir genes are identical. Actually genes of the I region are responsible for several functions, as detected in either in vivo or in vitro assays. In order to determine whether different functions are expressions of the activities of the same or of different chemical entities, it will be necessary to isolate and determine the structure of the active substances. Investigators are beginning to elucidate the chemical nature of some of the materials in question, including the suppressor and helper factors and the Ia antigens.

Because the gene coding for the specific helper factor is located in the I region, Munro and Taussig hypothesized that the factor might be a product of the Ir gene for (T,G)-A--L that had been previously identified by McDevitt and Michael Sela of Weizmann Institute of Science in Rehovot, Israel. Although it might be predicted that T cells from strains of mice that respond poorly to (T,G)-A--L would not produce the factor, Taussig and Edna Mozes of the Weizmann Institute showed that T cells from one strain of low-responding mice produced as much factor as T cells from high responders. The defect in the response therefore appeared to reside in the B cells.

The question of the type of cell in which Ir genes are expressed is a critical one. If the products of the genes are the receptors for antigen on T cells, then the products must necessarily be found in T cells. The fact that Ir genes affect only responses in which T cells participate is evidence in favor of the hypothesis that the genes might code for the receptors. But when investigators tried to find out where the genes were expressed, some, including those at the Weizmann Institute, found that the B cell was the site of the gene action, whereas others found that the T cell was.

McDevitt belongs to the latter group. In one set of experiments, he used tetraparental mice obtained by fusing very early, undifferentiated embryos of high and low responder strains and transplanting the chimeric embryos into foster mothers where they develop until they are born normally. The B cells of both strains can survive in the same animal despite their antigenic differences. McDevitt then measured antibody production in response to the antigen (T,G)-A--L, and found that B cells of the low responder strain produced just as much antibody as those of the high responder type. When he obtained the chimeras by fusing embryos of two different low responder strains there was little or no increase in antibody production in response to (T,G)-A--L. According to McDevitt, these results would indicate that the inability to respond does not reside in the B cells. He favors the hypothesis that the product of the Ir gene for (T,G)-A--L is expressed in T cells where it may serve to recognize antigen.

Evidence for Two Ir Genes

More recently, several groups of investigators have acquired evidence that two distinct Ir genes, one expressed in T cells and the other in B cells, are needed in order for an animal to mount an immune response to some antigens. These findings help to reconcile some of the diverse results about where Ir genes are expressed, although the results of McDevitt's experiments with the chimeric mice cannot be reconciled by them. Moreover, the findings provide a scheme to explain the collaboration between T and B lymphocytes.

Munro, Taussig, and Mozes examined the capacity of T cells from several strains of low responder mice to produce the helper factor and of B cells to respond to it. They found three patterns. The T cells from some of the strains produced the factor but the B cells did not respond to it; T cells from other strains did not produce the factor but the B cells responded to factor produced by other strains; and there was one strain in which the T cells did not produce the helper factor, nor did the B cells respond to it.

The other investigators who have evidence indicating that two genes are needed to control immune responses include Benacerraf and his colleagues, who have found that such is the case for a synthetic polypeptide consisting of glutamic acid, lysine, and phenlyalanine; Mozes and Sela, who identified two genes participating in the response to a polypeptide of tyrosine, glutamic acid, proline, and lysine; and Klaus Rajewski and his colleagues at the University of Cologne, who found that two genes located in the MHC of the mouse regulate the immune response to the enzyme lactate dehydrogenase.

The picture emerging from all this is one in which there are actually two kinds of Ir genes, instead of just a single type. The T cell carries the product of one of them; this product serves as both the receptor that recognizes antigen, and, when released from the T cell, as the activator (or suppressor) of B cell activities. The other would be expressed in the B cell where it may act as an acceptor for the regulators released by T cells. As required by the clonal selection theory, each T cell would carry receptors for only one antigen but each B cell would have acceptor sites for, and could respond to, all regulators.

Although many investigators think that this model is a major step toward clarification of the mechanism of interaction between T and B cells, they do not think that it completely solves the problems. For example, the model is based mainly on evidence garnered from only one system, that is, the one involving production of a helper factor involved in the response of mouse lymphocytes to (T,G)-A--L. Katz and D. Amerding of Harvard Medical School have identified another helper factor that is produced by T cells and appears to act on B cells. This factor, in contrast to those described previously, is not specific for antigen. Additional work is needed to determine whether these models for T and B cell interactions are general. There is also the possibility that the two genes needed for an immune response may be expressed in different subpopulations of T cells or in T cells and macrophages.

Another unanswered question concerns the nature of the Ia antigens and whether they are the products of the Ir genes or are merely very closely associated with those products. Studies of the distribution of the Ia antigens on different cell types have shown that they are found in large quantities on B cells and a few other cell types, but only in traces or not at all on T cells. Recently, however, McDevitt and his colleagues have fractionated both T and B cell populations into subpopulations and determined which carry Ia antigens. McDevitt says that most of the T cells lack the antigens but that suppressor T cells have them. Helper T cells may also carry Ia antigens but further confirmation of this is required because other investigations have not found the antigens on helper T cells. Thus, only a small proportion of the total T cell population carries the antigens but the ones that do are the ones involved in interactions with B cells. The Stanford investigators have also identified at least two subpopulations of B cells on the basis of whether or not they bear Ia antigens.

Although the correlation between the distribution of Ia antigens on B and T cell subpopulations and the expression of Ir gene functions suggests that the Ia antigens may be the molecules mediating Ir gene effects, other explanations are possible. The Ia antigens might instead function primarily in interactions between cells whereas separate Ir genes might be in-

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public interest science. He was, he recalls, "upset" by NSF's "negative" reaction to the meeting but adds that friends have told him that the Foundation is now taking a more positive approach.

Kennedy's original intention was to legislate the Science for Citizens program in NSF's 1976 authorization bill, but he ran into trouble when the House was not willing to agree to a proposed $5 million budget for a new program whose nature was vague, to say the least. But the House was willing to go along with a requirement that the NSF "prepare a comprehensive plan for the establishment and conduct" of such a program. Furthermore, Congress decreed that "This plan is to be prepared with full public participation. . . ." Hence, the seven open hearings.

Although Congress was not quite sure specifically how it wanted a Science for Citizens program to operate, it did give NSF some general ideas about what to be thinking about, and NSF passed them along in a "Dear Colleague" letter it sent to hundreds of scientists and citizens' groups throughout the country. The tentative purposes of the program, as Congress spelled them out, are three: (i) to improve public understanding of public policy issues; (ii) to encourage scientists, engineers, and students to participate in activities aimed at the resolution of public policy issues; and (iii) to enable nonprofit citizens' public interest groups to acquire technical expertise to assist them in dealing with scientific and technological aspects of public policy issues.

Anybody wanting to testify at one of NSF's hearings on how the program should be put together had to submit a written statement before getting on the agenda but was allowed to do so as late as the afternoon before the hearing. Even so, some public interest groups complained that the requirement for a written statement is, as the National Council for Public Assessment of Technology put it, "precisely the type of restriction that inhibits citizen groups from participation in government proceedings." Nevertheless, scores of them testified.

According to NSF officials and individuals from the Association of Science-Technology Centers (ASTEC), which handled the arrangements for the hearings, some of the testimony was very helpful and some of it missed the point. There was a lot of testimony to the effect that NSF should educate the public about science, with no emphasis, stated or implied, on science policy, which is the point of it all. Thus, one NSF official concluded that "an awful lot of the public can't read"—an observation that did not inspire in him enthusiasm for public participation in NSF's business.

Although NSF officials insist that they are still "boiling down" the information they have gathered and, therefore, cannot say what they will put in their report to Congress, they are willing to make a few general statements about what they've got. According to Harvey Averch, acting assistant director of the Directorate for Science Education, it is highly unlikely that NSF will go to Congress with a tightly drawn plan. Rather, he says, it "will probably recommend options and say to Congress, 'Let's talk about this.' "

Averch is not sure that NSF will want to launch a program to fund public interest groups and gives a couple of reasons. One is the "real concern" within the Foundation and among Science Board members about dealing with a new and unpredictable constituency. Another is the matter of being caught in a position of the government, through NSF, funding an organization that might turn around and sue some other part of the government. "It is not NSF's business to take sides, directly or indirectly, on policy issues," Averch declares.

An alternative to direct funding of public interest groups that is being considered as an option to present to Congress would be to establish and maintain a national register of scientists willing to volunteer their expertise to moneyless citizens groups, much as lawyers do pro bono work. "We might keep names of such scientists but we would not certify them in any way, just list them."

The Foundation is already somewhat involved in supporting shows for Public Television (the NOVA series is a prominent example) and it might propose expanding support to encourage shows dealing explicitly with policy rather than the substance of science.

Another option that might be proposed is the establishment of regional science centers designed to identify science-related issues of importance to the community and to provide expert information on them. There was a good deal of testimony recommending such centers, with speakers suggesting everything from the creation of a few centers to one in every congressional district. Several individuals suggested that science museums and other science centers that are part of ASTEC would be a sensible place to start.

Whatever emerges, it is a safe bet that any NSF Science for Citizens effort will be programmed for a modest beginning to allow the Foundation time to get the hang of what one official, with measured understatement, said would be a "new adventure for us."—BARBARA J. CULLITON

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volved in specific antigen recognition. For example, William Paul of NIAID has proposed such a model in which Ia antigens and Ir gene products, although combined in a single polypeptide chain, constitute separate regions with their own individual functions. The model is based on observations by Paul, Shevach, and Ira Green, also of NIAID, that the Ia and Ir genes appear to be linked but nevertheless distinct genes, and that the products of the two types of genes are closely associated on cell surfaces. This model is analogous to that for immunoglobulin structure and function.

The implications of the research on Ir genes are not just theoretical; these studies may also contribute to a better understanding of human disease. A number of investigators have shown associations between certain human diseases and specific histocompatibility antigens. Most of the diseases involve defective or inappropriate immune responses, and many are thought to be of autoimmune origin; that is, they may be caused by an attack of the immune system on the body's own tissues. They include ankylosing spondylitis, Reiter's disease, psoriasis, Graves' disease, multiple sclerosis, and ragweed hayfever.

Ankylosing spondylitis is a disease related to rheumatoid arthritis in which the spine becomes inflamed and may eventually become rigid and immobile. The association between this condition and the B27 histocompatibility antigen is particularly strong. According to Derrick Brewerton of Westminster Hospital in London and Lee Schlosstein of Wadsworth Veterans Administration Hospital in Los Angeles, more than 90 percent of patients with the disease carry the antigen whereas only 7 percent of the general population does.

Although human Ir genes have not been as thoroughly studied and mapped as those of the mouse, they are also known to be closely linked to histocompatibility antigens. Thus, many investigators think that the association between diseases and histocompatibility antigens may actually represent an association between the disease and Ir genes. The presence or absence of genes controlling the capacity to make immune responses could obviously have a great deal to do with disease susceptibility.

—JEAN L. MARX

Additional Readings

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