Suppressor T Cells: Role in Immune Regulation

Killer, helper, suppressor: one class of cells—the T (for thymus-derived) lymphocytes—plays all these roles. As mediators of cellular immunity, activated or killer T cells can directly attack and destroy foreign antigens including those on cell surfaces. In addition, T cells are involved in regulating the activities of other cells of the immune system. The other major class of lymphocytes, the B (for bone marrow) cells, needs the cooperation of helper T cells in order to respond with antibody production to many antigens.

More recently, investigators have recognized yet a third functional type of T cell—the suppressor—that can inhibit antibody production by B lymphocytes. Suppressor T cells are important because of their function as regulators of immune responses and because there is evidence that either an excess or deficiency of these cells can result in serious disease.

Investigators have used a number of different methods to demonstrate the suppressive effect of T cells on immune responses. In general, they show that a particular response, such as production of an antibody against a particular antigen, is completely or partially reduced in the presence of T lymphocytes. The response may then increase when the T cells are removed or destroyed.

A system under investigation by Richard Gershon and his colleagues at Yale University School of Medicine involves the induction of immunological tolerance in mice. Animals are said to be immunologically tolerant when they have lost the capacity to make an immune response to an antigen as a result of previous exposure to the antigen. The Yale group showed that they could not induce tolerance to sheep red blood cells (SRBC) in mice that had been deprived of their T cells but could if the animals' T cells were replaced. The tolerant mice had cells with the capacity of making antibody against SRBC; however, they did not make it, even when given T cells from nontolerant animals.

The spleen contains large numbers of T lymphocytes. If spleen cells were transferred to normal mice from tolerant animals, the recipients also became tolerant. Spleen cells treated with an antiserum that specifically destroys T cells did not confer tolerance on the recipient mice. These results imply that T cells are needed to suppress the immune response of tolerant animals to SRBC and that, once tolerance is induced, the suppressive T cells will prevent the activities of nontolerant cells that would normally act as helpers. Since production of antibody against SRBC requires the cooperation of helper T cells, either the helpers or the B cells could be the target of the suppressor T cells.

According to Gershon, antigenic competition also depends on the presence of T lymphocytes. Antigenic competition occurs when the immune response to one antigen suppresses the subsequent production of antibody against a second, unrelated antigen.

Phillip Baker and his colleagues at the National Institute of Allergy and Infectious Diseases have evidence not only for suppressor T cells in the system they are studying but also for yet another functional class of T lymphocytes called "amplifier" cells. By their definition, amplifier cells are not required for antibody production, as helper cells may be, but under appropriate conditions will enhance it.

These investigators use a polysaccharide isolated from type III pneumococcal bacteria to evoke an immune response in mice. Synthesis of antibody against this antigen does not require the participation of helper T cells. They found that treating the animals with antiserums against lymphocytes or thymocytes (ALS or ATS), both of which destroy T cells, increased the response of the animals to the antigen. Infusion of syngeneic (of the same genetic constitution) thymocytes abrogated the enhancement.

Mice that are homozygous for the "nude" trait lack thymus glands and, consequently, functional T lymphocytes. Baker found that although these animals produce slightly more antibody against the bacterial antigen than do normal mice, treating them with ALS did not enhance the response. Baker interprets these results as indicating that normal mice have amplifier cells, which, in the absence of suppressors, increase the response to the antigen. Since athymic mice of the "nude" strain have neither suppressors nor amplifiers, ALS does not increase their response.

A number of explanations for the greater effect of ALS on suppressor than on amplifier T cells have been suggested by Baker. They include the possibilities that the two types of cells are located in different sites so that the amplifiers are less accessible to ALS, that fewer amplifier cells are needed for activity, and that the surface antigens of the suppressors make them more susceptible to destruction by ALS.

Tomio Tada of the Chiba University School of Medicine in Japan and Ko Okumura, currently at Stanford University Medical School, have studied some very specific suppressor effects of T cells. The antigen they use is dinitrophenol (DNP) linked to a carrier protein extracted from a certain species of roundworm. The investigators found that several treatments that deplete the T cell populations of rats greatly enhanced the production of antibodies against the antigen. Tada and Okumura could then suppress the enhancement by treating the animals with thymus or spleen cells from animals that had been hyperimmunized with the same DNP-protein complex. Cells from untreated rats or rats hyperimmunized with a complex of DNP and a different protein had no effect on the enhancement.

One of the criticisms of the concept of the suppressor T cell is the possibility that the suppressive effects may in fact be directly attributable to the production of the antibodies themselves. Antibodies can be immunosuppressive. Tada and Okumura, however, washed the cells they injected several times to remove contaminating antibodies. This eliminates the possibility that the suppression they observed was due to the administration of antibodies rather than to the T cells.

"Chronic" allotype suppression is another immunological phenomenon that involves the activities of suppressor T cells, according to Leonore Herzenberg and Leonard Herzenberg of Stanford University Medical School. Allotypes are alternate forms of an immunoglobulin that are genetically determined. The investigators mate female BALB/c mice carrying one form of the immunoglobulin they are studying with males of the SJL/L strain (a strain having a number of severe immunological abnormalities) that carry another. Normally, the hybrid progeny will have both allotypes; however, if the

females are immunized with the paternal form before mating, the production of paternal allotype will be completely or chronically suppressed in more than half the progeny by the time they are 6 months old.

The Herzenbergs showed that an active factor associated with T lymphocytes is responsible for chronic allotype suppression. They irradiate BALB/c mice to destroy the animals' immune system and prevent graft rejection, and then inject them with spleen cells from unsuppressed hybrid progeny. The injected spleen cells produce both maternal and paternal allotypes. However, when a mixture of equal numbers of normal and suppressed hybrid spleen cells are injected, much less of the paternal allotype is produced. In fact, the cells produce as little as do chronically suppressed spleen cells when only they are injected. Treating the suppressed spleen cells with an antiserum that destroys T cells destroyed the suppressing activity, which again shows that T cells can prevent antibody production.

Thus, T cells can suppress antibody production in a number of experimental systems. Many investigators are coming to the conclusion that this suppression is essential for normal control of immune responses. If that is the case, then malfunction of that control could result in either an excess of antibodies, as in allergic reactions, or production of aberrant antibodies, such as the autoantibodies found in autoimmune conditions, or a lack of antibodies and consequent immunodeficiency.

The immune system does not normally attack the body's own tissues, but occasionally this tolerance for self is lost and autoimmunity results. A number of severe debilitating diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE), are thought to be autoimmune conditions. One of the characteristics of these diseases is the presence of autoantibodies, that is, antibodies against self.

Many investigators think that suppressor T cells normally prevent the production of autoantibodies and that a deficiency of suppressors may therefore contribute to the etiology of autoimmunity. For example, Alfred Steinberg and his colleagues at the National Institute of Arthritis, Metabolism, and Digestive Diseases, and Norman Talal of the University of California Medical Center in San Francisco, have found that there is a progressive decrease with age in suppressor effects in New Zealand Black (NZB) mice. This strain of mouse is frequently used by investigators studying autoimmunity because the animals spontaneously develop a disease that closely resembles SLE in humans.

According to Steinberg, as NZB mice age, they give an increased antibody response to immunization with pneumococcal polysaccharide, the same bacterial antigen used by Baker. There is no such increase in the response of another strain of mice that is not subject to autoimmune disease. The fact that thymus cells from young NZB mice reduced the excessive antibody response of the older animals supports the hypothesis that it is caused by loss of suppressor T cells. Steinberg also observed a decrease in cell-mediated immunity as NZB mice aged.

The losses of suppressor functions appear before other thymic functions decrease in NZB mice and before the onset of autoimmune symptoms. The cause of the loss of suppressor T cells is unknown. Viruses and genetic factors probably play a role. Investigators have also suggested that a deficiency of thymic hormones may be involved (*Science*, 28 March, p. 1183).

Having too many suppressor T cells can be just as harmful as having too few, according to Thomas Waldmann and his colleagues at the National Cancer Institute. They have been investigating an immunodeficiency disease called common variable hypogammaglobulinemia that is characterized by inability of the affected individual to make adequate quantities of antibodies.

This disease, like certain other immunodeficiencies, may be caused by intrinsic defects in B cells or their precursors that prevent them from maturing into antibody-secreting cells or that block synthesis and release of antibodies. The NCI group, however, showed that lymphocytes from at least one group of patients inhibited antibody secretion by cultured lymphocytes of normal individuals who had been stimulated with pokeweed mitogen. Pokeweed mitogen is a lectin, that is, a plant protein that can mimic the natural effects of antigens by stimulating

Astronomers Steer Students Away

In spite of the difficulties that new Ph.D.'s in astronomy have finding jobs, the ranks of astronomy graduate students are still growing rapidly, according to a recent study by the National Academy of Sciences. The astronomy manpower committee, chaired by Leo Goldberg at Kitt Peak National Observatory, advised that the production of new Ph.D.'s be reduced and found that many of them had received insufficient diversification in their graduate work, especially with respect to physics courses. The committee took the unusual step of recommending that the standard letter excerpted below be sent to all prospective astronomy students.

Dear Student:

Traditionally, the most desirable positions for a young astronomer have been those at large universities or major observatories where one could devote a substantial fraction of time to research. However, the increased numbers of graduate students in the physical sciences, the overall decreased enrollment at the undergraduate levels, and the decreased funds available for research have combined to make the prospect of obtaining such positions increasingly difficult. Opportunities will be available, of course, but the ratio of candidates to available positions at current rates of Ph.D. production is projected to be more than 4 to 1.

You should now seriously consider whether your interest in the field is so great that you wish to devote five more years of hard study to astronomy, knowing that at the end of those years the main job openings will probably be in fields entirely different from astronomy.

With the subject matter of the physical sciences changing so rapidly, it is not uncommon for a person who acquires knowledge and research experience in one field to change later to an allied one. The positions which will be available to you will be filled on a highly competitive basis, and you must be very honest with yourself in assessing your chances of success not only for completion of the Ph.D. but also in the competition for employment. We will do everything possible to advise you carefully as to your chances for future success in both graduate school and your intended career.

For the teachers of astronomy, a review of the graduate curricula and attitudes toward student job prospects were recommended.—W.D.M.

differentiation and division of B cells into antibody-secreting cells.

It is possible to partially separate T and B cells. When Waldmann and his colleagues did this with lymphocytes from one of the immunodeficient patients, the fraction that was enriched with B cells produced significant amounts of antibody in vitro. Unpurified lymphocytes from such patients produce little or no antibody. These results indicate that lack of antibody secretion in some patients with common variable hypogammaglobulinemia is due to the effects of suppressor T cells rather than to an intrinsic defect in the B cells of the patients.

A number of questions remain to be answered about suppressor T cells and their activities. One of the most important is whether one cell can perform both helper and suppressor functions or whether they are accomplished by two distinct populations of T cells. If they are distinct, then it might be possible to manipulate the two populations independently—a capability that could facilitate therapeutic applications of the knowledge gained by these studies. There is evidence for both points of view.

Among those who think that helper and suppressor T cells are distinct is Richard Dutton of the University of California in San Diego. He is studying the effects of concanavalin A (Con A), another lectin, on the activities of spleen cells. He finds that, under some conditions, Con A inhibits antibody production by mouse spleen cells in response to SRBC. A number of treatments, including use of an antiserum against T cells, abolishes the inhibition. With the inhibition abrogated, Con A will then stimulate the response of the cultured cells to SRBC. Dutton said that the characteristics of the inhibition are consistent with it's being caused by a subgroup of T lymphocytes called T_1 cells, whereas another subgroup, the T_2 cells, appear to be responsible for the stimulatory effect.

As further evidence for two distinct groups of cells, Dutton sites experiments in which he has demonstrated a direct competition between cells treated to make them act as suppressors and others that act as helpers. Adding the helpers abolishes the inhibitory effects of the suppressors on antibody production; adding the suppressors prevents the stimulatory effects of the helpers. Other investigators have suggested that suppression may result from an excess of helper T cells but Dutton's experiments are inconsistent with that idea.

The Herzenbergs have also demonstrated competitive effects between helper and suppressor T cells in their system. They think that B cell activity may be regulated by the balance of the activities of helper and suppressor T cells.

In contrast, Gershon thinks that suppressors and helpers are the same cells. He has proposed what he calls the "second law of thymodynamics." It states that for every helper T cell effect, there is an equal and opposite suppressor effect. He has described five examples of experimental systems in which a regulatory T cell population alters the response of another T cell population. In all cases in which the responding population was highly active, the regulator suppressed it; when the activity of the responders was low, the regulatory cells augmented it. Gershon suggests that the regulator T cell receives signals of some kind—possibly antibodies or antibody-antigen complexes. A high signal level causes the regulator to suppress the activity of the responder and turn off the signal. Suppressing helper T cells, for example, would ultimately decrease antibody production by B cells. Faint signals produce the opposite effect. But only one kind of regulator cell would be needed.

Suppressor T Cells and Tumor Growth

In early experiments, Gershon has found that suppressor T cells allow the growth of some experimentally transplanted tumors. They could do this by preventing the activities of the killer T cells thought to destroy tumor cells. Some investigators think that tumors produce blocking factors, possibly large quantities of antigen-antibody complexes (*Science*, 3 May 1974, p. 553), to prevent this normal process of immune surveillance. Gershon hypothesizes that these complexes signal the suppressor T cell to inhibit activity of the killer cells.

Separation of the different subgroups of T cells would enable investigators to study their properties individually and determine whether one cell class can act as both helper and suppressor. A new instrument, the fluorescence-activated cell sorter (FACS), developed by the Herzenbergs and their colleagues may permit just that. The investigators have separated some classes of T cells and are now characterizing them.

Another question is whether suppressors act on other T cells or on B cells or on both. Gershon thinks that they act on T cells, and only indirectly on B cells. As a result of kinetic studies on the rate of formation of antibody-forming cells from the B cell precursors, Baker thinks that the suppressors act primarily by limiting the extent to which B cells proliferate in response to antigen and thus limit antibody production.

Although some T cells function as killers, the Herzenbergs think that suppressors are not killers and may belong to a different subclass of lymphocytes. They have shown that the suppressors do not kill the B cells that give rise to the cells producing the paternal immunoglobulin allotype. These investigators found normal numbers of B cells carrying the paternal immunoglobulin on their cell surfaces in chronically suppressed animals. They isolated them with the FACS and showed that the isolated cells include memory cells that, when properly stimulated in the absence of suppressors, multiply and complete differentiation to cells that secrete the paternal allotype form.

At present, the Herzenbergs are uncertain as to whether the suppressors act on helper cells or on B cells, but they favor the former as the site of action. They have recently completed a series of experiments that indicate that the suppressors decrease allotype production by decreasing helper activity. Since the suppression is highly specific for the paternal allotype, this implies the existence of specific helper T cells. The Herzenbergs say that additional evidence is necessary to confirm this hypothesis.

It is possible that the regulator cells secrete substances that turn other cells on or off. Tada and his co-workers have isolated one protein from spleen cells and thymocytes that can inhibit production of antibody to a specific antigen and another that stimulates it.

The immune system, with its plethora of effectors and mechanisms, is so highly complex that the researchers using different systems to study suppression may actually be investigating somewhat different phenomena. This complicates current attempts to synthesize their results into a coherent picture of suppressor cell activity. Investigators think, however, that this very complexity will enable them to derive more information from their experiments and will eventually result in a precise understanding of suppressor cell functions. Nevertheless, unraveling the regulatory events in immune responses obviously will not be an easy task.

—JEAN L. MARX