IMMUNOLOGY

Mounting a Targeted Strike on Unwanted Immune Responses

The immune system is not the kindest of hosts. It flat out hates strangers, indiscriminately killing both helpful and harmful visitors shortly after check-in. It also abuses its own kin, occasionally savaging a pancreas or a nerve cell for no good reason. Considering the nasty characters that drop in now and then, most people accept the dark side of these behaviors. But immunologists do not. They have long been using crude tools to try and modify the errant behavior. Yet as immunologists gain a finer understanding of the immune system, they are designing ever-more sophisticated pulleys and levers that may in the future prevent transplant rejection and such debilitating autoimmune diseases as diabetes, myasthenia gravis, and rheumatoid arthritis. On pages 789 and 792, two separate studies reveal that the future is closer than you might imagine.

The two research groups—one led by Peter Linsley of Bristol-Myers Squibb Pharmaceutical Research Institute in Seattle and the other by Jeffrey Bluestone of the University of Chicago Medical Center's Ben May Institute—venture into previously unexplored immunologic terrain with a new drug, CTLA4Ig, that aims to shut off unwanted immune responses. Says Ron Schwartz, head of the Laboratory of Cellular and Molecular Immunology at the National Institute of Allergy and Infectious Diseases: "This is a whole new way of treating transplantation and autoimmune diseases." No, CTLA4Ig has not been tested in human trials. But it appears potent, has yet to exhibit any serious toxicity in animal tests, and Schwartz has high hopes that it will eventually be a big gun in the immunosuppressive armamentarium, which now includes cyclosporine A, FK506, and monoclonal antibodies—all of which can cause serious side effects.

It's easiest to understand CTLA4Ig's function by looking at transplantation. When a tissue is excised from one person and stitched into another, "antigen presenting cells" offer bits of the stranger—the antigen—to the host's T cells. This interaction sends a critical signal to T cells that, when combined with a second "costimulatory" signal, activates them. Activation, in turn, triggers production of antibodies and killer T cells that rid the body of the foreigner.

Researchers have known for some time that, in test-tube experiments, interrupting the second signal causes T cells to lapse into a state of anergy that prevents them from reacting to a given antigen. This, then, hijacks the cascade of events broadly known as the immune response.

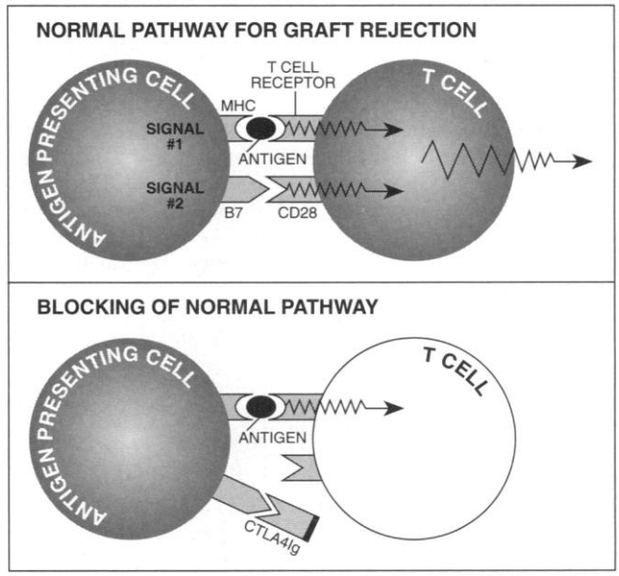
And this is where CTLA4Ig, the brainchild of Linsley and co-workers at Bristol-Myers Squibb, fits in. The second signal is sent when B7, a molecule on the surface of the antigen presenting cells, binds to receptors that stud the surface of the T cells, called CD28. Last year, Linsley's group found that another T cell surface molecule, called CTLA-4, also binds to B7. And CTLA-4, it turned out, had a greater affinity for B7 than did CD28, which it closely resembles. So the group engineered a soluble form of CTLA-4 to study its function. That soluble form is CTLA4Ig, a hybrid of CTLA-4 and immunoglobulin. As luck had it, CTLA4Ig also bound B7 and blocked its binding to CD28 and thus the costimulatory signal.

Next Linsley and his colleagues tried CTLA4Ig in mice, showing that, as expected, it powerfully suppressed antibody responses, which they report in this issue. The researchers injected mice with the drug shortly after immunizing them with two different foreign antigens. Though CTLA4Ig suppressed antibody production in both cases, it unfortunately didn't induce permanent tolerance to either antigen. Still, the work suggests that CTLA4Ig may be able to modify autoimmune diseases in which antibodies cause the destruction.

Another CTLA4Ig paper in this issue takes the concept one step further. At the University of Chicago, Bluestone and Deborah Lenschow grafted human pancreatic islet cells, which produce insulin, into the kidneys of diabetic mice. Some mice treated with CTLA4Ig had intact grafts for more than 90 days before being sacrificed, while control animals rejected the grafts after 6 days. Subsequent experiments showed that the treated mice would, without any further CTLA4Ig treatment, accept new islet grafts from the same donor. The implication: CTLA4Ig induced donor-specific tolerance—the Holy Grail of transplant immunology.

As Bluestone sees it, the beauty of CTLA4Ig is that it simultaneously blocks a costimulatory signal and allows the T cell to meet and thereby remember its encounter with the antigen. The end result is that whole populations of "bad guys"—in this case, T cells directed against the donor graft—are rendered ineffective against that antigen.

Similar work is under way at the University of Michigan's Howard Hughes Medical Institute, where in a study now under review, Craig Thompson and cohorts transplanted rat hearts from one species to another. Untreated transplant recipients rejected their new hearts within 8 days. But rats injected with CTLA4Ig for 7 days after receiving a transplant did not reject their grafts for 18 to 43 days. "As long as we treat the animals, they do not seem to reject the heart," says Thompson. But the animals need continued treatment to avoid rejection, an impractical strategy because a prolonged state of immunosuppression puts the body at too great a risk.



Two to tango. When a soluble molecule blocks one of two costimulatory signals to a T cell, the immune response is stymied.

Charles Janeway Jr. of the Yale University School of Medicine and the Howard Hughes Medical Institute, who studies immune system activation, says the simple message from all of these experiments is "that you need more than antigen to get graft rejection"—an observation being borne out by work on several different fronts. In this case, that "more" is the signal sent out when B7 and CD28 unite. Though Janeway suspects that CTLA4Ig may end up being a valuable supplement to other immunosuppressants, he's still cautious. "What this does is tell you there's an opportunity," he says. "It doesn't tell you how to seize that opportunity." Indeed, researchers working with CTLA4Ig say a few years of animal studies lie ahead before the drug is ready for human trials.

–Jon Cohen