CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Transplantation without immunosuppression: What the future may hold

CHARLES G. OROSZ, PHD
Professor of Surgery, Pathology, and Medical Microbiology; Director, Clinical Histocompatibility Laboratory; Director, Transplant Sciences Program, Division of Transplantation, Ohio State University

ABSTRACT

Research in noncompliant allograft recipients and in a murine model has led us to hypothesize that it may be possible to exploit the phenomenon of linked antigen recognition in human organ transplantation. If this approach proves successful, it may ultimately allow transplant recipients to avoid taking immunosuppressive drugs long-term.

IN A MEDICAL MYSTERY, a few lucky transplant recipients who stop taking their immunosuppressant medications still manage to avoid rejection and keep their transplanted organs. The mechanism by which this happens is not yet clear, but research into it could lead us to the Holy Grail of transplantation—treatments to block rejection without powerful immunosuppressant drugs.

At the center of this research is a phenomenon called "linked recognition." Simply put, when the immune system is exposed to an antigen in the presence of selected experimental immunosuppressant drugs, it will tolerate that antigen when it sees it again—*and it will tolerate any other antigen that it sees in the company of the original antigen.*

Here is how the treatment might work. Before transplantation we would give the recipient immunosuppressant drugs and expose him or her to some exotic antigen that is not likely to be encountered in daily life, thus causing the recipient to accept the antigen. Then, at the time of transplantation, we would again provide the antigen at the graft site. Through the process of linked recognition, the immune system would down-regulate its response to the antigen—and hopefully, to the transplant itself.

At this point, this approach is far from reality. I will discuss some of the concepts and research in this area.

THWARTING ACUTE REJECTION

Heart transplants in mice typically function for only about a week if the mouse receives no immunosuppressant drugs, due to an inflammatory process that resembles acute transplant rejection in humans. Several experimental agents, if given for approximately the first month after transplantation, can prevent this acute rejection; these include monoclonal antibody to CD4 (an antigen on helper T cells), monoclonal antibody to vascular cell adhesion molecule, and gallium nitrate.[1]

If successful, this work could lead us to the Holy Grail of transplantation

No matter which of these agents is used, after it is stopped the animals do not acutely reject the organ. They develop histologic changes in their transplants that resemble those seen in chronic transplant rejection in humans: local inflammation, donor-reactive T-cell immunity, donor-reactive alloantibody production, and vascular remodeling. However, this chronic rejection process is "smoldering" rather than aggressive, and some of the mice can survive without more immunosuppressant drugs well into old age.

Acceptance or tolerance? It would be misleading to say that these mice *tolerate* their transplanted hearts—tolerance implies a total absence of an immune response. Rather, we believe they *accept* their transplants in an

active, alloprotective process. We call these mice "allograft-acceptor" mice.

TESTING LINKED RECOGNITION

In another experiment to directly test the concept of linked recognition,[2] we gave mice subcutaneous injections of tetanus toxoid. Two weeks later we gave the mice heart transplants and treated them with gallium nitrate to promote graft acceptance.

Sixty days later, we gave all the mice subcutaneous injections of tetanus toxoid, spleen cells from the graft donor, or both. Later, we checked the injection sites for swelling, which indicates a delayed-type hypersensitivity reaction.

As expected, sites injected with tetanus toxoid developed swelling, whereas sites injected with donor spleen cells did not. However, sites that were injected with both tetanus toxoid and spleen cells failed to develop swelling, indicating that the mice "accepted" the tetanus toxoid that had been "linked" to the accepted graft antigens.[3,4] In theory, the therapeutic process in humans would be to run this system backwards, ie, use an antigen to promote graft acceptance.

This patient may have developed alloprotective immunity to his allograft

CLINICAL APPLICATIONS

Do humans develop similar linked-recognition mechanisms? The first step in finding out would be to look for such a mechanism in successful long-term transplant recipients—especially those few who stop taking their immunosuppressant drugs but do not reject their transplanted organ.

We developed a trans vivo assay to do this. In this procedure, we take mononuclear cells from the peripheral blood of these patients and place them subcutaneously in the pinnae or footpads of mice, along with the challenge antigens.[5]

If the mice receive cells from antigen-sensitized humans, they develop a local swelling that resembles delayed-type hypersensitivity within 24 hours. This test effectively identifies humans who have delayed-type hypersensitivity, even if they are being treated with immunosuppressants.

In collaboration with Will Burlingham at the University of Wisconsin, we recently tested a noncompliant renal allograft patient in this manner. We found that when test mice were injected with the patient's mononuclear cells and tetanus toxoid, they developed swelling. But when administered the patient's mononuclear cells with cells from the patient's donor, the mice did not develop swelling. Also, swelling did not occur in response to tetanus toxoid or donor cells if both of them were given together.

This finding indicates that the patient may have developed alloprotective immunity to his donor alloantigens, which allowed him to retain his allograft without pharmacologic immunosuppression. It also suggests that we can use this assay to identify similar lucky individuals.

WHAT DOES THE FUTURE HOLD?

We are just in the early stages of discovering the underlying mechanisms in linked recognition. However, if our line of research works, it would have tremendous implications for transplantation.

CME ANSWERS

Answers to the CREDIT TEST on page 447 of this issue

1 **A** 2 **D** 3 **C** 4 **D** 5 **B** 6 **A** 7 **A** 8 **C** 9 **A** 10 **E** 11 **B** 12 **C**

REFERENCES

1. **Orosz CG, Wakely E, Sedmak DD, Bergese SD, VanBuskirk AM.** Prolonged murine cardiac allograft acceptance. Characteristics of persistent active alloimmunity after treatment with gallium nitrate versus anti-CD4 monoclonal antibody. Transplantation 1997; 63:1109–1117.
2. **Sirak J, Orosz CG, Wakely E, VanBuskirk AM.** Alloreactive delayed-type hypersensitivity in graft recipients: complexity of responses and divergence from acute rejection. Transplantation 1997; 63:1300–1307.
3. **Madsen JC, Superina RA, Wood KJ, Morris PJ.** Immunological unresponsiveness induced by recipient cells transfected with donor *MHC* genes [letter]. Nature 1988; 332:161–164.
4. **Davies JD, Leong LYW, Mellor A, Cobbold SP, Waldmann H.** T cell suppression in transplantation tolerance through linked recognition. J Immunol 1996; 156:3602–3607.
5. **Carrodeguas L, Orosz CG, Waldman WJ, Sedmak DD, Adams PW, VanBuskirk AM.** Trans vivo analysis of human delayed-type hypersensitivity reactivity. Hum Immunol 1999. In press.