Transferred Immune Cells May Help Fight Viral Infection

When it comes to fighting off viruses, people pretty much have to depend on their immune systems. And if those immune defenses aren't up to the job—because they've been suppressed by the drugs needed to treat cancer or prevent organ rejection, for example, or by diseases such as AIDS—then a virus that might otherwise have caused little harm can produce serious, even fatal, infections. Now comes a research team led by Stanley Riddell and Philip Greenberg of the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle with new results, described on page 238, suggesting that it may be possible to restore the immune response to a common virus in immunosuppressed patients. The key is a transplant of immune cells that specifically attack cells infected by the virus.

Further work with more patients will be needed to see how effectively the treatment protects them against infection, Greenberg says, but the initial results are encouraging. The Seattle group has not only succeeded at growing the large number of specifically targeted immune cells needed for the immunotherapy, but they have also shown that, once transferred, the cells can persist for a long time in humans and retain their activity. What's more, the treatment is nontoxic and can be given on an outpatient basis.

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The achievements lead immunologist Drew Pardoll of the Johns Hopkins Medical School in Baltimore to describe the work as "among the most exciting advances in human immunotherapy since people started exploring it." And besides pointing to ways of protecting immunosuppressed patients from infection, he adds, the work may also help in designing immunotherapies against the underlying diseases, AIDS and cancer, somewhat along the lines also being explored by cancer specialist Steven Rosenberg, chief of surgery at the National Cancer Institute (NCI).

Greenberg, Riddell, and their colleagues are working with patients who are immunosuppressed because they have undergone bone marrow transplants as a treatment for leukemia. During a window of 30 to 100 days after the patients' own cancerous marrow has been destroyed with radiation and before the transplanted marrow takes hold and grows new immune cells, the patients are particularly vulnerable to infection from pathogens. One of the major threats, striking about 50% of the transplant recipients, is cytomegalovirus (CMV), which can cause a fatal pneumonia.

Because CMV is such a problem for bone marrow transplant recipients and other immunocompromised people, Greenberg says, 10 years ago researchers, including Ullrich Koszinowski at the University of Ulm in Germany, Thomas Braciale of the University of Virginia Medical Center in Charlottesville, as well as the Seattle group, began developing mouse models to test the feasibility of a stopgap transfer of immune cells from healthy individuals to immunocompromised ones that would confer immunity to CMV.

The first question the researchers faced was which set of immune cells was most effective at warding off CMV. In the mice, the "killer" T cells proved to be best at protecting against the murine equivalent of the disease. In a study conducted on bone marrow recipients last year, the researchers found that the same cells are key to CMV resistance in people. None of the patients who came down with CMV infections, the researchers found, had recovered their ability to produce killer T cells directed against the virus; and conversely, all of the patients who did have these cells remained free of the infections. Those results gave the Greenberg lab the impetus to press on.

In the current study, the team took a sample of T cells from each of three people who were donating bone marrow to leukemia patients and separated from each sample only those killer cells that seek out and destroy cells infected with CMV. After growing large numbers of these CMV-specific T cells in lab cultures, the researchers injected them into the corresponding marrow recipients, in four weekly doses, with the last dose containing 1 billion cells.

The patient responses so far have been good, Greenberg says. No one suffered any toxic reactions as a result of the cell infusions. And the transferred cells not only persisted up to 12 weeks after the last infusion, but they retained their specificity and remained capable of killing CMV-infected cells. "This represents a real demonstration that you can put antigen-specific killer T cells into people," says Greenberg. What's more, none of the patients came down with CMV infections. Greenberg cautions, however, that three patients do not provide statistically meaningful data regarding protection and a larger study will have to be conducted.

While similar therapeutic strategies for adoptive immunotherapies have been an interest of immunologists for some time, they've been hampered by the CMV-specific cells' tendency to lose their specificity for the virus. Notes Pardoll, "It is much easier to lose antigen specificity than to retain it." What made the difference this time, says Riddell, is that "we invested a lot of time working out the culture conditions."

Growing on their own. The researchers found they had to first expose the growing T cells to CMV-infected cells in order to maintain specificity and then the cells had to be cultured with the growth factor interleukin-2 to get them to reproduce. This cycle of exposure to antigen followed by growth stimulation with interleukin, notes Riddell, had to be repeated several times until adequate numbers of T cells were accumulated, which takes between 6 and 12 weeks. Because this process is too cumbersome for widespread use, Greenberg says, the team is exploring improved strategies, including one in which the killer cells are outfitted with a gene for the growth factor so they can stimulate their own growth after they've been transferred and encounter antigen in their new host. If this can be done, it would mean that cells would not have to be administered as often to maintain protection.

More efficient strategies for transferring immune cells could prove a boon if other potential applications of the therapy pan out. "There are obviously other diseases where lack of immunity comes into play," says Greenberg. And indeed, the group anticipates transferring killer T cells directed against an HIV protein into an AIDS patient within the next 2 months, hoping the cells will combat the virus. The technique might also be useful in cancer therapy, where the killer T cells could target proteins displayed on the surfaces of tumor cells and therefore attack the tumor, a strategy similar to that of NCI's Rosenberg.

The killer T cells used by Rosenberg, however, are directed toward many different tumor antigens. Such cells may have an advantage, he points out, because cells within the same tumor may display different surface antigens, and the highly specific T cells used by the Greenberg group could miss tumor cells that a mixed population of T cells would kill. Still, he concedes, Greenberg's approach may have the advantage of producing a more potent population of killer T cells. How effective either approach will be remains to be seen. As Rosenberg notes, "we are just at the infancy of the development of these treatments."

–Michelle Hoffman