Immune Attack on Cancer

Researchers spur the immune system to rout malignancies

By KATHLEEN FACKELMANN

Abnormal cells often grow silently in the body. In most cases, though, they never get a chance to develop into cancer. The immune system homes in on these overly prolific cells and annihilates them first.

The cancers that people become aware of occur when aberrant cells somehow evade the immune system and continue to divide aggressively. If left unchecked, such cells form a malignant tumor.

Now, medical researchers have recruited a specialized cell from the immune system into the battle against cancer. A Swiss and German team has published results of a study in which this strategy successfully targeted the deadly skin cancer melanoma. A U.S. team used the same immune therapy to treat prostate cancer, the second leading cause of death in men in the United States.

"These studies are demonstrating that it may well be possible to immunize against cancer," says Steven A. Rosenberg of the National Cancer Institute in Bethesda, Md. Rosenberg has also tested an immune therapy on melanoma patients, with promising results.

Such immune strategies are sometimes called cancer vaccines. Traditionally, vaccines prime the body to fight off an infection before it gets started. Cancer vaccines, in contrast, rev up the immune system to rout an existing disease.

Researchers suggest that the vaccines will provide an alternative to chemotherapy, in which doctors give patients round after round of cell-killing drugs in the hope of destroying all the malignant cells. Chemotherapy may control a cancer for a time, but in many cases, cancerous cells break off from the main tumor, travel through the bloodstream, and eventually spread the disease.

Since the 1980s, researchers looking for a different approach have been laboring to find ways of boosting the immune system's response to cancer. Their hard work is finally starting to pay off. "It's not just a pipe dream," says Harmon Eyre, chief medical officer of the American Cancer Society (ACS) in Atlanta. "There's evidence now that this is working."

The element of the immune system that shows the most promise for cancer therapy is the dendritic cell, a type of white blood cell.

Cancer cells make proteins not usually found in healthy cells. Fragments of those abnormal proteins are called peptides and appear on the surface of the malignant cell like a red flag. Dendritic cells typically prowl the bloodstream in search of dead or dying cells. When it finds such a cell, the dendritic cell gobbles up the cellular debris and sprints to the lymph nodes, the command center of the immune system. This action has led Michael T. Lotze of the University of Pittsburgh to call dendritic cells the "track stars" of the immune system.

Immune therapy may target a malignant cell more precisely than chemotherapy's drop-the-bomb approach.

Upon reaching the lymph nodes, the dendritic cell, which has a number of arms, holds out the cancer cell peptide—much as a runner would pass a baton in a relay race. The other white cells scan the peptide, and those best able to kill the cancer cell proliferate rapidly, forming an army of killer T cells. Released into the bloodstream, the defenders seek out the flagged cancer cells and trigger a self-destruct mechanism in them. In effect, the T lymphocytes force the cancer cells to kill themselves.

Many cancers, unfortunately, evade recognition by dendritic cells and thus avoid an immune-mediated death. Recent experiments with cancer vaccines have attempted to encourage dendritic cells to take notice of a masked cancer threat and sound the alarm.

Melanoma, a cancer that is on the rise in many countries, including the United States, has been a target of potential immune therapies for almost a decade. Frank O. Nestle of the University of Zurich Medical School and Dirk Schadendorf of the University of Heidelberg in Germany recently used dendritic cells to attack melanoma, a cancer of the pigment-producing skin cells

The ACS predicts that more than 41,600 people in the United States will be diagnosed with melanoma this year. If caught early, melanoma is one of the most curable of all cancers. If it has spread, it is often deadly.

Schadendorf's team recruited 16 men and women with melanoma. All had been treated with a variety of standard therapies, including chemotherapy, radiation therapy, and surgery, but their cancer continued to spread aggressively.

The researchers obtained dendritic cells from each patient's bloodstream. To encourage those cells to zero in on the malignant cells, they concocted a cocktail of the harvested dendritic cells and appropriate tumor peptides. In such close quarters, the immune cells had no choice but to recognize these cancer markers.

In four cases, the researchers didn't have purified peptides to mix with the dendritic cells. Instead, they ground up bits of the patient's tumor and combined that tissue with the dendritic cells.

They hoped that dendritic cells treated in this fashion would, once injected back into the bloodstream, hunt down the cancer cells and initiate a vigorous immune attack.

To test that approach, the researchers took each customized solution of treated dendritic cells and injected it into the patient's lymph nodes or under the skin, weekly at first and then at longer intervals.

Surprisingly, 2 of the 18 people showed no trace of cancer more than a year after treatment began, Schadendorf says. Three others had a significant response—their tumors shrank by more than half. Such advanced cases of melanoma almost never show spontaneous remission and are considered incurable by traditional methods. Yet Schadendorf says that it's not clear what the results mean, even for the two people who remain tumorfree.

"We have to wait for a longer time to see if the response is close to a cure," he explains. Schadendorf and his colleagues published their results in the March NATURE MEDICINE.

The team described a number of innovative procedures, including injecting the cancer vaccine directly into the lymph nodes, comments Lotze. "It looked like they enjoyed extraordinary responses," he told SCIENCE NEWS.

Also in March, Lotze described preliminary results from his group's trial of dendritic cell therapy for melanoma. The Pittsburgh group treated 21 people with advanced melanoma. They injected dendritic cells that had been mixed with cancer markers.

"We now have three patients who have had prolonged stability," Lotze said at

the American Association for Cancer Research (AACR) meeting in New Orleans. "So far, we've seen no evidence of growth of their tumors," added team member Joseph Baar. One patient's tumor disappeared altogether, "and now, for all intents and purposes, she's been diseasefree for over a year," says Baar.

Cancer of the prostate, the gland that produces the cloudy liquid that goes into semen, is less often deadly than melanoma, but it is far more common. An estimated 184,500 men will be diagnosed with prostate cancer this year.

Seattle scientists Michael L. Salgaller of Northwest Biotherapeutics, Gerald P. Murphy of the Pacific Northwest Cancer Foundation, and their colleagues have used dendritic cell therapy to target cancer of the prostate. The team recruited 33 men with prostate cancer that had spread to other sites in the body. For these men, traditional treatments—surgery, radiation, and hormone therapy—had failed to contain the disease.

The researchers took blood samples to obtain dendritic cells. They then mixed the cells with two peptides. The dendritic cells took up the peptides and displayed them. Once a week for 6 weeks, each patient received an intravenous infusion of the solution.

The team reports that in 9 of the 33 men, the treatment halted the spread of their disease. These patients showed a 50 percent decrease in prostate-specific antigen (PSA), a protein that rises as prostate cancer advances. They also experienced a substantial drop in the amount of cancer that had made its way into the bones, Salgaller says.

In another 10 patients, the disease stabilized. In these cases, the marker fell less than 50 percent, and the cancer in bone decreased slightly.

The remaining men did not respond to the treatment, and their prostate cancer continued to spread.

"I think we're having a very promising impact on the progression of disease," Salgaller says. "We have now an important percentage who are either responding to therapy or whose disease has stopped progressing." Nonetheless, he adds, the results need to be confirmed in a larger number of patients. The researchers presented their findings at the AACR meeting and at the ACS-sponsored Science Writer's Seminar held in March in Newport Beach, Calif.

Eyre comments that Murphy and Salgaller have "some evidence that this is working in some men. That's a huge step forward."

Eventually, the researchers plan to offer the therapy to men with less advanced prostate cancer to see whether in such cases a revved up immune response will actually seek out and destroy all of the cancer cells.

Scientists are now extending immune therapy beyond prostate cancer and melanoma to other types of malignancies, including breast and ovarian cancer.

One benefit of the treatment is that, in most cases, it doesn't trigger the deleterious side effects of traditional therapies. Chemotherapy, for example, is a crude treatment that poisons all rapidly dividing cells, including healthy cells, and thus provokes vomiting and hair loss. The side effects of immune therapy are typically milder: a low-grade fever and some aches and pains.

Although many cancer patients would gladly undergo the rigors of chemotherapy to achieve a cancerfree future, that outcome is by no means certain. For many people, the cancer still wins the war. Cancer vaccines may offer a more effective way of attacking the disease. Proponents argue that immune therapy can target a malignant cell more precisely than chemotherapy's drop-the-bomb approach.

Researchers have seen a handful of dramatic responses to immune therapy, but so far, such responses have been limited to melanoma. This cancer may be more vulnerable to the immune system's blitzkrieg than other malignancies, says Dawn Willis, director of research promotion at ACS. Although melanoma can be widely disseminated, individual tumors are small. In addition, this cancer strikes people in the prime of life, when their immune systems are likely to be robust, she says.

It's uncertain whether researchers can extend such dramatic responses to other cancers and thus more patients. Schadendorf believes that some malignant cells will continue to hide from the immune system, even when confronted with a souped-up solution of dendritic cells. His team hopes to find a way to block cancer cells trying to escape the immune attack.

While the side effects of cancer vaccines have appeared modest so far, investigators still have concerns. The peptides employed by many researchers as targets may also be present on a small number of healthy cells, Eyre says. Moreover, no one knows whether immune therapy could induce the body's immune cells to attack healthy cells. Only larger trials will prove the ultimate safety of this approach, he adds.

In spite of the potential pitfalls, cancer vaccines have entered a new era. Researchers are testing them on larger groups of people, and if all goes well, the vaccines could gain federal approval within 5 years. Approval would pave the way for widespread therapeutic use.

"I've been in this field 20-some years," Lotze says. "There's as much, if not more, excitement about this than anything I've seen previously." □