The Dark Side of Tumor-Fighting Protein

A human protein that has been highly touted, in genetically engineered form, as a potential anticancer drug has been found to be essentially identical to another body protein, cachectin, that causes debilitating weight loss in people with chronic infection or cancer. And in a separate study, cachectin is also reported to be a major cause of bacterially induced shock.

Reports in the Aug. 30 SCIENCE detail cachectin's role in weight loss through the inhibition of fat storage cells, as well as its role in the onset of shock. The protein's striking similarity to tumor necrosis factor (TNF), which is nearing U.S. anticancer trials with humans, was reported in the Aug. 8 NATURE.

The fat cell finding was a collaboration between laboratories at Rockefeller University in New York City and Stanford University. The researchers applied cachectin, which is produced by infection-fighting white blood cells, to mature fat cells and found that the cells lost their fat-synthesizing and storage potential. They also observed a reversible decline in the expression of genes that play an active role in the development of fat cells.

Deemphasizing fat storage frees up energy, says Frank Torti, one of the Stanford researchers, who speculates that the protein mobilizes energy to fuel the body's fight against infection or cancer. But when the condition becomes chronic, "what was once a benefit becomes a problem," he says, and the person loses weight even when food intake remains constant.

In the second study, three Rockefeller University researchers injected mice with a bacterial protein that can induce shock. They found they could block the effect by blocking the action of cachectin. "We think it [cachectin] is one of the major causes of shock," says Anthony C. Cerami of Rockefeller.

"We think if you have small amounts it is good because it mobilizes energy for the immune system," says Cerami. But when the immune system can't get rid of the invader, cachexia — wasting — ensues. And in an overwhelming infection, the cachectin causes shock, he says.

Cerami and his colleagues report in NATURE that human TNF and mouse cachectin are nearly identical; human TNF and human cachectin are completely identical, he says.

Cerami suspects the ability to kill cancer cells is not the factor's major role in the body. "It's probably much more important in facilitating the fight against infection, which is a much more common occurrence," he says.

The work points out potential toxicities in cachectin's twin, TNF, says Torti, "but what's predicted in tissue culture models vis-à-vis what happens to people can be very different." Human trials with TNF have already begun in Japan, and reportedly a slight fever has been the only side effect.

Finding the proper dosage will be key, Cerami says. "Losing weight for one week won't hurt that much," he says. "The limiting factor will be shock."

A spokesperson for Genentech, Inc., in South San Francisco says that some animals in their preliminary TNF trials lost weight but gained it back after the study. The company hopes to begin human trials this fall, she says.

Alfred Rudolph, a clinical researcher at Cetus Corp. in Emeryville, Calif., says the cachexia and shock findings don't affect Cetus's plans to develop TNF as an anticancer agent. The company is creating slightly modified versions of the protein and hopes to begin clinical trials in 1986. Eventually, says Rudolph, they may work on the protein as an anti-obesity factor.

Dan Longo of the National Cancer Institute in Bethesda, Md., where clinical trials with TNF could begin in late fall, says that since side effects will be carefully monitored, the reported findings won't affect the clinical trial. The findings, he notes, suggest other ways to use TNF, such as employing an antibody to the protein to prevent shock. *—J. Silberner*

Researchers identify 'cancer anorexia'

Some cancer patients appear to develop a specific type of anorexia that is not a direct effect of chemotherapy or the tumor itself but rather a "learned aversion" to specific foods they associate with their treatment or illness, according to a University of Washington at Seattle psychologist. Moreover, says the researcher, Ilene L. Bernstein, there is evidence that because the condition is behavioral as well as physiological, it can be at least partially corrected simply through a change in diet.

"Cancer patients develop aversions to foods eaten just *before* chemotherapy," Bernstein said last week in Los Angeles at the annual meeting of the American Psychological Association. "But we found that they will eat other foods."

Weight and appetite loss have historically been major problems with many such patients, and have generally been assumed to result directly from both the nausea-producing effects of chemotherapy and the chemical changes triggered by the tumor, says Bernstein. These mechanisms "clearly play a role" in cancer anorexia and in other cancer-related weight loss (see above), she acknowledges. But her research also indicates that not only do the learned aversions to chemotherapy-associated foods exist but "that tumor growth may also suppress appetite indirectly by producing chronic symptoms which act as ... stimuli in the acquisition of learned food aversions."

In the chemotherapy-related portion of her study, Bernstein looked at a total of 120 children receiving chemotherapy as outpatients at a Seattle clinic. One group of children was exposed to a "novel"-flavored ice cream just prior to therapy, a control group received no ice cream and another group received ice cream but not drugs. Two to four weeks later, the children were given a choice between eating the same ice cream or playing a game. "Patients in the experimental group were much less likely to choose to eat the ice cream than were patients in either control group," Bernstein reports. "Thus children will avoid eating a food which has previously been associated with...toxic chemotherapy."

In a separate study, rats implanted with tumor tissue and a control group of tumorless rats were first given continuous access for several days to a "complete rodent diet." Then, for 24 hours, they were given a choice between that diet and a novel one. "Tumor-bearing animals had developed a pronounced aversion to the [complete] diet, the diet available during recent tumor growth," says Bernstein. But, she adds, "we saw striking elevations in food intake...when an alternate food was available."

While these results "confirm" a learned food aversion, Bernstein suggests that because the aversion occurs only with certain tumors, there may also be a physiological component at work. Evidence indicates that this may involve the tumor's production of excessive toxins or hormones or its depletion of nutrients from the body. In either case, she says, it is theoretically possible to "balance" the system through diet, drugs or supplements.

She has already begun an intervention study with chemotherapy patients, using the novel ice cream as a "scapegoat taste" just prior to treatment. Preliminary results suggest that sacrificing one such food will enable patients to eat other foods and possibly prevent the anorexia. *—J. Greenberg*