Antibody halts cancer-related wasting condition: Study pinpoints a molecular cause of cachexia

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New research raises the prospect of more effective treatments for cachexia, a profound wasting of fat and muscle occurring in about half of all cancer patients, raising their risk of death, according to scientists from Dana-Farber Cancer Institute.

Many strategies have been tried to reverse the condition, which may cause such frailty that patients can't endure potentially life-saving treatments, but none have had great success.

Scientists reporting in the July 13 advanced online edition of *Nature*, led by Bruce Spiegelman, PhD, demonstrated that in mice bearing lung tumors, their symptoms of cachexia improved or were prevented when given an antibody that blocked the effects of a protein, PTHrP, secreted by the tumor cells. PTHrP stands for parathyroid hormone-related protein, and is known to be released from many types of cancer cells.

The scientists said their findings are the first to explain in detail how PTHrP from tumors switches on a thermogenic (heat-producing) process in fatty tissues, resulting in unhealthy weight loss.

This tumor-derived protein, they found, stimulated "beige" or brown fat cells mixed with stored white fat in the body, causing the white fat to "brown" – that is, generate heat and cause weight loss even when the animals were at rest.

The researchers carried out two experiments using mice that developed lung tumors and cachexia. In one, they administered a polyclonal antibody that specifically neutralizes PTHrP and found that it prevented the wasting almost completely, while untreated animals became mildly cachexic.

In a second experiment, the antibody treatment prevented the loss of muscle mass and improved muscle function, while control animals developed severe muscle-wasting.

"You would have expected, based on our first experiments in cell culture, that blocking PTHrP in the mice would reduce browning of the fat," said Spiegelman. "But we were surprised that it also affected the loss of muscle mass, and improved health."

The research suggested that PTHrP alone doesn't directly cause muscle wasting, yet blocking the protein's activity prevents it.

Thus, the role of PTHrP "is definitely not the whole answer" to the riddle of cachexia, noted Spiegelman, but may be a necessary part, while other factors are also involved.

A collaborator on the study, Vickie E. Baracos, PhD, at the University of Alberta in Edmonton, Canada, provided the blood of 47 patients with lung or colon cancer who were cachexic. Serkan Kir, PhD, from the Spiegelman lab – and first author on the paper –found increased levels of PTHrP in 17 of the patients. Those patients had significantly lower lean body mass and were producing more heat energy at rest than were the other patients in the group.

It may turn out that the PTHrP mechanism is responsible for cachexia in a subset, but not all, cancer patients, Spiegelman suggested. Before trying the anti-PTHrP antibody in human patients, he said, "clinicians

would probably first want to find out if the protein is elevated in certain cancers, and determine which patients would be good candidates for a clinical trial."

Barrett Rollins, MD, PhD, Dana-Farber's chief scientific officer, commented that the report from Spiegelman and his colleagues "provides a new roadmap for developing a rational, mechanistically based treatment for this incredibly debilitating condition that occurs in such a large number of our patients. Until now we've had no truly effective way to reverse this horrible complication."

Patients with upper gastrointestinal and pancreatic cancers are the most likely to develop cachexia, and the condition affects about 80 percent of terminal cancer patients. Current strategy is to give appetite stimulants and nutrient supplements, along with medications to counteract some of the molecular pathways believed to underlie the wasting process, but with limited success.

More information: Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia, *Nature*, DOI: 10.1038/nature13528

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