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Possible treatment for deadly weight loss

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Many cancer patients are susceptible to potentially lethal weight loss. Now researchers understand better why this happens, and perhaps how to prevent the condition. "Our goal is to know more about what happens in cancer patients who develop rapid and severe weight loss," says Geir Bjørkøy, a professor in the Department of Bioengineering at the Norwegian University of Science and Technology (NTNU).

Doctors have known about this serious complication affecting cancer patients for a long time. The ancient Greeks called it cachexia, meaning "bad condition."

Many cancer patients develop cachexia. An estimated 20 to 30 per cent of those with the condition may die of it and not from their tumors.

For many of these cancer patients, reduced food intake cannot explain the weight loss and it cannot be reversed by eating more. The results from this research have recently been published in the journal *Scientific Reports*, and the researchers hope these results can help affected patients.

Inflammation is a factor

Since cachexia is a serious condition common in cancer patients and as a "side effect" of many other life-threatening diseases, researchers have been trying to find the underlying causes in order to develop possible treatment.

Although cachexia has long been recognized as an adverse effect of

cancer, medical doctors and researchers still don't fully understand what is happening in these patients, Bjørkøy says. Based on numerous and varied studies, we know that this disturbance in the body's metabolism is due to systemic inflammatory reactions.

In cancer patients, it is known that cancer cells or tumors trigger this immune response, because the condition can disappear if the tumor is removed. Unfortunately, tumors often cannot be removed, and researchers would like to find other strategies to prevent this wasting condition from developing in the first place.

Muscles disappear

Cachexia is characterized by a specific type of weight loss where muscle mass breaks down. This muscle loss can occur with or without a loss of fat.

In normal weight reduction, fat degrades before muscle proteins do. Bjørkøy's research has therefore specifically addressed two questions:
First, what substances do cancer cells or tumors secrete that trigger muscle mass loss?
And second, what process is activated in the muscle that causes muscle mass loss?

Since researchers haven't known which process was being triggered, it has been challenging to determine the stimulating factor or factors.

Two processes

Two main processes break down proteins in our body's cells: proteasomes and lysosomes.

Proteasomes are small tubes containing enzymes. Single proteins can be unfolded and threaded down into the proteasomes like strands from a ball of yarn. The protein strand is then cut into small pieces (peptides) and single amino acids that are released from the tube and reused. The capacity of this destruction system appears to be limited.

Lysosomes, by contrast, have a great capacity to degrade biomolecules, both materials taken up from the cell's outer surface and from inside the cells. Lysosomes are small spherical vesicles inside our cells that are full of digestive enzymes. Several hundred of these small digestive vesicles can exist inside each cell.

Lysosome membranes need to be intact so that the digestive enzymes don't leak out. When lysosomes degrade components from the inside the cell, the process is called autophagy, or "self-devouring."

Attacks itself

Bjørkøy and his colleagues' hypothesis was that the loss of muscle mass in cachexia patients was due to increased cell autophagy. This hypothesis would mean that the accelerated autophagy should come from factors that the cancer cells or tumours secrete and that distribute throughout the body.

After analyzing blood samples from several hundred cancer patients and healthy donors, the researchers found that the blood samples from cancer patients can contain autophagic stimuling compounds that may be associated with weight loss in patients.

Cultured cancer cells were found to do the same thing – they secreted compounds that stimulated autophagy in other cells, including muscle cells.

Then researchers discovered that the cancer cells were also secreting the pro-inflammatory cytokine IL-6 and that this factor itself accelerates autophagy in other cells.

The experiments also showed that a special form of IL-6 signalling can induce autophagy in many different cells in the body.

May be important for treatment

The findings may be important for future treatment of cancer patients affected by weight loss, because new drugs are available that can block uncontrolled IL-6 signalling between cells in the body.

Alternatively, the results suggest that weight loss can be reduced by autophagy inhibitors like chloroquine, which has long been used to treat malaria.

NTNU's Centre for Molecular Inflammation Research (CEMIR) and the university's Faculty of Natural Sciences led the research for this study in close collaboration with researchers and clinicians from St. Olavs Hospital, Haukeland University Hospital/UiB, Edinburgh and Switzerland.

The study also used tests from the Nord-Trøndelag Health Study (HUNT), and collaborated closely with researchers in the international pharmaceutical company Novartis in Basel.

More information: Kristine Pettersen et al. Cancer cachexia associates with a systemic autophagy-inducing activity mimicked by cancer cell-derived IL-6 trans-signaling, *Scientific Reports* (2017). DOI: 10.1038/s41598-017-02088-2