# Towards a treatment for cancer cachexia

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*Cachexia is a very serious and incurable debilitating condition that commonly affects cancer patients. The discovery of a mechanism responsible for the muscle atrophy that accompanies cachexia, however, suggests drug development for this debilitating condition.*

People with certain types of cancer, especially those bearing gastrointestinal and lung tumors, frequently suffer from cachexia, which is severe weight loss accompanied by muscle atrophy.

As their muscles weaken, those affected become extremely vulnerable to injuries, infections, and side effects from treatments, causing their condition to deteriorate significantly. It is estimated that up to 30% of cancer-related deaths are a direct result of cachexia (1).

## METABOLIC REPROGRAMMING

During evolution, our bodies have adapted to the presence of injury or disease by producing inflammatory substances that stimulate catabolism - the breakdown of cell molecules.

The release of stores of fatty acids and amino acids helps provide essential elements for tissue repair and fight infections, two phenomena essential to maintain organ function. After tissue is repaired and infections are cleared, inflammation subsides and this catabolism decreases, which helps replenish the body's stores.

This balance is completely disrupted in cancer patients, however, as the presence of tumors creates persistent inflammatory conditions, much like an injury that fails to heal.

The breakdown of fats and proteins in the muscles then continues unabated, leading to very serious weight loss which can lead to death.

## FAULTY SIGNALING

Recent research has identified a mechanism that plays a key role in this cachexia associated with cancer (2).

Using a model of cachexia where implantation of a colorectal tumor causes rapid muscle atrophy, the researchers found that this deterioration of the muscles was associated with a disruption in the signal of a family of growth factors called bone morphogenic proteins (BMPs).

Under normal conditions, these proteins stimulate the growth of muscle cells as well as their adequate connections with the motor nerves which trigger their contraction.

In cachexia conditions, on the other hand, the presence of inflammatory molecules coming from the tumor causes the production of another protein, called Noggin, by the muscle cells which blocks this signal, which at the same time prevents the growth of the muscle and causes its atrophy.

The researchers also observed that this inhibitory protein disrupted the interaction of muscle cells with motor nerves and that this blockage was also involved in the accelerated breakdown of muscles.

These mechanisms are believed to be involved in cachexia in cancer patients, since analysis of muscle biopsies from patients with colorectal or pancreatic cancer revealed an increase in the levels of the Noggin protein, as well as the presence of denervation of muscles.

An interesting point of the study is the finding that administration of tilorone (a synthetic molecule that activates the BMP pathway) prevented weight loss and muscle atrophy and significantly increased survival. This, even though that molecule had no direct impact on cancer cells. It therefore appears that targeting this protein could represent a valid therapeutic strategy to reduce the devastating impact of cachexia and significantly improve the quality of life of cancer patients.

(1) von Haehling S and SD Anker. Cachexia as a major underestimated and unmet medical need: facts and numbers. J. Cachexia Sarcopenia Muscle 2010 ; 1: 1-5.

(2) Sartori S et al. Perturbed BMP signaling and denervation promote muscle wasting in cancer cachexia. Sci. Transl Med. 2021 ; 13: eaay9592.

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