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## Cancer

# Tumours block protective muscle and nerve signals

Teresa A. Zimmers

Certain cancers cause people to weaken and waste away. A mouse model of this points to tumour-induced blockade of molecules that normally protect muscle innervation and mass. Will the discovery lead to therapies for this deadly condition?

People who have certain types of cancer, particularly gastrointestinal and lung tumours, frequently experience what is called cachexia<sup>1</sup> – a progressive and often severe weight loss, irrespective of the level of food intake. This condition arises when tumours rewire the body's neural, immune and metabolic systems to trigger the breakdown (catabolism) of adipose tissue and skeletal muscle<sup>2,3</sup>. As their muscles grow weaker and smaller, affected individuals lose their ability to function normally. They become vulnerable to injury, infections and treatment toxicities, and then ultimately fail to respond to cancer treatment.

Even though cachexia causes more than 30% of all cancer deaths<sup>4</sup>, and is prevalent and deadly in many other conditions, including organ failure, there are no effective approved therapies. Pre-clinical animal studies demonstrate that blocking muscle wasting preserves function and lengthens life, with or without anti-tumour therapy<sup>5</sup> – which suggests that the same might also be true for people with cancer who are at risk of cachexia. Writing in *Science Translational Medicine*, Sartori *et al.*<sup>6</sup> identify a targetable pathway for cancer-associated cachexia (Fig. 1), bringing us closer to developing a treatment.

To counter disease and injury, animals have evolved mechanisms that include inflammatory signals alerting the central nervous system to reduce appetite and food-seeking behaviours – an adaptation that limits vulnerability to predators. The same signals drive the process of catabolism, which liberates stores of fatty acids and amino acids to repair tissue, fight infection and protect brain and organ function. Once tissues are repaired and

infections cleared, inflammation subsides and normal feeding resumes, allowing replenishment of the body's reserves. However, cancer co-opts these survival mechanisms, turning these useful adaptations into a source of harm. Tumours, which can be considered both a type of regenerative tissue and a non-healing wound, do not subside over time in the way that a typical injury or infection does. So the catabolism of fat and muscle proceeds unabated, often leading to emaciation and death.

How tumours trigger these changes is beginning to be unravelled. Signals, yet to

**“No treatments exist for cachexia, which can be fatal.”**

be fully identified, that emanate from the tumour (or arise from the host response to the tumour) are received by muscle cells. In the muscle, these signals activate the catabolism of proteins. In part, this happens through a process of destruction known as the ubiquitin-proteasome system, which depends on specific enzymes that tag proteins for degradation. This leads to the characteristic shrinking of muscle fibres and wasting of muscle throughout the body seen in cachexia.

A decrease in the size of muscles and muscle fibres (atrophy) can also be triggered for other reasons. They include reduced quality, activity or number of the neurons that innervate muscle to control voluntary motor movement (a condition referred to as denervation), as occurs in motor neuron diseases such as amyotrophic lateral sclerosis.

Each of these mechanisms is also proposed to contribute to muscle wasting in cancer<sup>7</sup>.

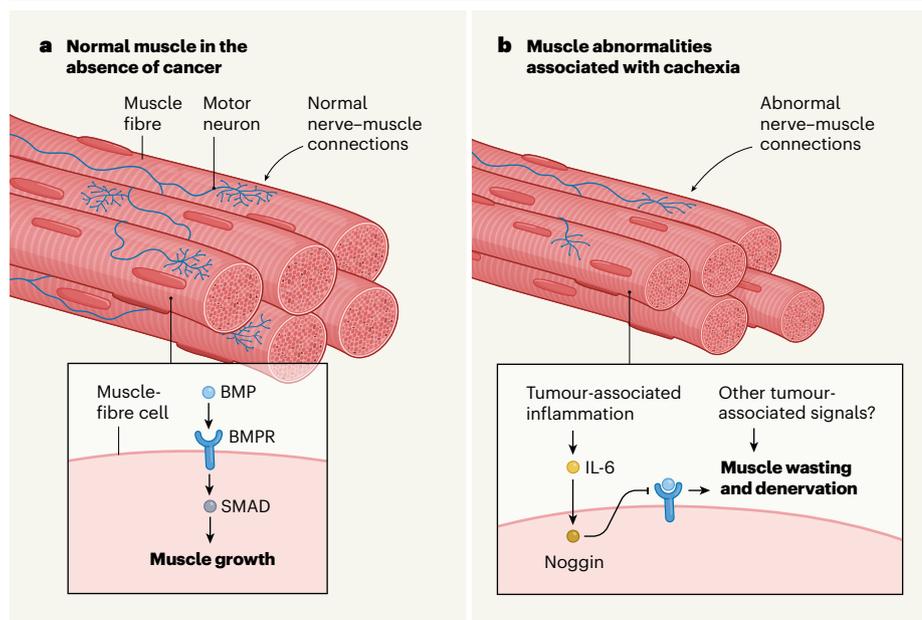
Sartori and colleagues' study is a collaboration between research groups that previously identified<sup>8,9</sup> a series of molecular interactions known as the BMP pathway as a positive regulator of muscle function and mass. BMPs are secreted proteins that signal among cells and between tissues<sup>10</sup>. During development, these proteins specify the pattern and fate of tissues in the embryo. In adults, BMPs have essential roles in musculoskeletal health. They act on cells by binding receptors called BMPRs. This leads to the activation of SMAD proteins, which move to the nucleus to alter gene expression and, ultimately, cellular characteristics.

It was previously shown that a rise in BMP7 or BMPR activity promotes an increase in muscle size (hypertrophy) through SMAD1/5/8 proteins, and that BMP signalling is protective of muscle size in conditions of reduced innervation<sup>8</sup>. Earlier work has also established that BMP signalling through SMAD4 promotes muscle growth, and that the BMP inhibitor protein, Noggin, which blocks BMPR activation, induces muscle wasting<sup>9</sup>. These studies established BMP signalling as an important growth-promoting pathway in muscle. Sartori and colleagues have now investigated this pathway in the context of cancer-associated cachexia.

Studying a commonly used mouse model in which colon tumours inserted into an animal's flank lead to rapid and lethal muscle wasting, Sartori *et al.* document the activation of the ubiquitin-proteasome system and decreased BMP activity compared with the systems in mice without such tumours. The use of genetic approaches to increase BMP activity or to block Noggin blunted the activation of the ubiquitin-proteasome system and spared muscle in the mice with tumours. This evidence therefore indicates that tumour-induced Noggin impairs BMP signalling, leading to protein catabolism and muscle wasting.

Beyond the effects on muscle size, the investigators identify defective muscle innervation as preceding the loss of muscle mass, suggesting a causal role for denervation in cachexia. Using a combination of experimental approaches, the authors demonstrate that this defect was a loss of functional interaction between motor neurons and muscle cells (myofibres). This misalignment and degeneration of the neuron–myofibre connection could be mimicked by exposure to excess Noggin. Providing BMP or blocking Noggin were protective in this context.

What triggers this Noggin expression in muscle? Sartori *et al.* propose that it is the pro-inflammatory molecule IL-6. This protein helps to orchestrate the immune response and is tightly linked to cancer cachexia. Excess IL-6 induces cachexia, whereas IL-6



**Figure 1 | Pathways underlying muscle problems associated with cancer.** The condition cachexia is characterized by the severe weight loss and muscle wasting that is associated with certain types of cancer. No treatments exist for cachexia, which can be fatal. **a**, Previous work<sup>8,9</sup> indicates that the pathway mediated by BMP proteins, acting through the BMP receptor (BMPR) and SMAD proteins, promotes normal growth of muscle cells and their functional connections with motor neurons to enable normal muscle health and function. **b**, Sartori *et al.*<sup>6</sup> studied mouse models and clinical samples, and report that the low muscle mass of cachexia is associated with inhibition of the BMP pathway. This inhibition can be mediated by the protein IL-6, which is produced during the inflammation associated with cancer. IL-6 drives expression of the protein Noggin, which blocks the BMP pathway. The authors report that Noggin caused both muscle wasting and abnormalities in nerve–muscle connections, including fewer and weaker connections than usual between motor neurons and muscle fibres. Whether other tumour-associated signals also contribute to these phenomena remains to be determined.

inhibition blocks muscle wasting in mice with cancer<sup>11</sup>, although definitive clinical trials to assess this effect in humans are lacking. In the authors’ mouse model of cachexia, IL-6 triggered Noggin expression through activation of the protein STAT3. In this way, the authors establish the existence of a pathway that links tumour-induced inflammation with muscle degradation through the process of BMP inhibition.

Next, the team sought to determine the clinical relevance of certain findings. Using muscle taken from people undergoing surgery for colorectal or pancreatic cancer, the investigators demonstrate that people with cancer-associated cachexia show certain hallmarks similar to those observed in the model mice. These characteristics included higher average Noggin levels and increased activity of the ubiquitin-proteasome system; reduced myofibre size; and molecular, cellular and blood-borne evidence of denervation. Although IL-6 was not assessed, overall these results support a role for Noggin in cancer-induced muscle denervation and wasting in at least some of the people whose samples were analysed in the study.

Finally, the investigators examined the effects of a small molecule, tilorone, previously shown to increase BMP signalling in

lung cells<sup>12</sup>. In the cachexia model mice, BMP signalling in muscle was preserved in the animals that received tilorone. This treatment also blocked dysfunction of motor neurons, prevented weight loss and muscle wasting, and lengthened survival considerably – despite having no effect on tumour growth. Intriguingly, tilorone is said to have many effects beyond BMP activation (see [go.nature.com/3njce9](http://go.nature.com/3njce9)). These include antiviral and anti-inflammatory functions, as well as anti-fibrotic functions (targeting the condition called fibrosis, which is associated with the deposition of extracellular material and stiffening of tissue); activation of pathways associated with low levels of oxygen (hypoxia-inducible pathways)<sup>13</sup>; and potent and selective inhibition of the enzyme acetylcholinesterase<sup>14</sup>, which acts to end neuronal signalling events in muscles.

Given these diverse effects of tilorone, it is difficult to disentangle all of its potential mechanisms of action in this context, which might range from IL-6 inhibition (and consequently a reduction in Noggin expression) to direct preservation of the neuromuscular junction or improvement in food intake. However, this striking result should be followed up for further exploration in efforts to develop a potential therapy.

Sartori and co-workers present thought-provoking data linking Noggin, denervation and wasting. Nevertheless, given the small amount of data published on motor neurons in cachexia, and with some of the evidence conflicting<sup>15,16</sup>, a coordinated effort will be required to determine the frequency, magnitude and functional consequence of neuromuscular dysfunction in cachexia. Differences in tumour type, stage and host response or body condition (including age, sex, fitness and genetics) might dictate differences both in the activity of the BMP pathway and in the extent of motor-neuron degeneration and wasting in cancer. Interrogation of further models and careful analysis of larger numbers of samples from people with different tumour types should help to determine the universality of these observations.

Finally, approaches being considered to modulate this pathway must also address effects on other organs, on the tumour and on responses to anti-cancer therapy. Finding anti-cachexia therapies that complement anti-tumour therapies surely offers the best hope to people with this deadly condition.

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