Muscle and bone: new treatments for cancer-induced muscle weakness

Muscle weakness is a major clinical problem for patients with advanced cancer. In addition, chemotherapy itself can cause muscle weakness and this can persist for months or years after treatment, causing problems such as fatigue and falls which can lead to fractures and increased mortality. Muscle weakness can occur in the absence of weight loss or in the context of significant muscle wasting. Cancer patients with muscle depletion are also more prone to severe drug-associated toxicity and show a poorer prognosis overall. Currently there is no effective treatment for muscle weakness and the condition is not widely recognised by health care providers.

Tumours which metastasise or spread to the bone are common with many advanced cancers and affect 450,000 patients in the USA each year. Because bone and muscle are so closely interconnected and because muscle weakness is present in patients with these cancers, Dr David Waning and his colleagues began studying muscle weakness in animal models of bone metastasis.

Dr Waning, working with Dr Theresa Guise and Khalid Mohammad at the Indiana University School of Medicine, have unravelled one of the molecular mechanisms linking muscle weakness and cancer-induced bone resorption. Dr Waning is now focusing on the link between chemotherapy and muscle weakness.

THE RELATIONSHIP BETWEEN BONE AND MUSCLE

Historically much more attention has been paid to the physical interactions between bone and muscle than to the biochemical links between them. The bone is shaped by muscles, but bone also conversely affects the shape and size of muscles by providing an attachment site for locomotion. Bone and muscle are tightly connected during growth, and during ageing bone and muscle breakdown also occurs together. If one of the tissues is affected, the other is affected as well. More recently, a deeper appreciation for the molecular connections between bone and muscle has emerged.

The bone is a storehouse for minerals and various types of proteins. In healthy adults, bone is constantly broken down or built up in order to adjust for physical demands on the body or to repair tiny fractures that occur as a part of normal activity. Cells in the bone called osteoclasts, which break down and resorb bone, strike a critical balance to maintain homeostasis. When this balance is lost, such as during tumour growth in bone, abnormal new bone can be formed or overall bone loss can occur. When the mineralised bone matrix is broken down, proteins stored there can be released and passed onto the skeletal muscle and can have significant effects on muscle function.

Bone and muscle are two closely connected tissues yet the mechanisms linking them at the cell and molecular level are not well understood. Dr David Waning is an Associate Professor in the Department of Cellular and Molecular Physiology at the Penn State College of Medicine who studies the biochemical mechanisms that cause problems in these tissues during disease and ageing. His lab is developing new treatment approaches that aim to improve musculoskeletal health for cancer, ageing, and chemotherapy-induced conditions.

Bone-derived growth factors

Osteolytic factors

Osteoclasts

Metastatic cancer cells

Bone cells that metastasise to the bone can release osteolytic factors that stimulate the osteoclasts, bone-resorbing cells, to increase bone turnover. TGFβ, a cytokine released from the mineralised bone matrix by the activity of osteoclasts, drives a feed-forward vicious cycle of tumour growth in bone and leads to systemic skeletal muscle weakness.

The researchers’ data has shown that factors released from the bone matrix cause oxidative stress in muscle and that this is able to cause muscle weakness.

EXCESS BONE RESORPTION IMPAIRS MUSCLE FUNCTION

When certain cancers spread to the bone, tumour cells release proteins that aid their growth in bone and lead to the formation of more osteoclasts. The process of breakdown and resorption of bone by osteoclasts releases other proteins called growth factors from the mineralised bone matrix. One such protein growth factor is TGFβ, which stimulates tumour growth in metastatised breast cancer and stimulates further bone breakdown by osteoclasts. This results in a vicious cycle that leads to bone pain, fractures, excess calcium in the blood, pinched nerves and muscle weakness.

In research published in the journal Nature Medicine in 2015, Drs Waning and Mohammad, working with Dr Guise, looked at mouse models of human breast, lung and prostate cancers that had metastasised to bone and multiple myeloma in bone and found that the animals had impaired muscle function. This was not due to the presence of tumour cells in the muscle. The researchers then investigated whether muscle weakness caused by tumours that spread to the bone was due to a deficiency in muscle contraction or solely due to loss of muscle mass.

They found that TGFβ, when released from bone, caused levels of a protein called Nox4 to increase. Nox4 is a protein that creates reactive oxygen species (ROS), chemically reactive molecules that contain oxygen. ROS causes damage to the cell and oxidises proteins in the skeletal muscle. One of the targets of Nox4-induced oxidative stress is a protein critical for muscle contraction called RyR1, which functions as a channel for calcium. Collaborating with a team led by Dr Andrew Marks, at the Columbia University College of Physicians and Surgeons, they found that when RyR1 channels were oxidised they leaked calcium, resulting in these channels working incorrectly. As a result, muscle contraction, which depends on calcium, was not able to proceed properly.

The researchers also showed that TGFβ was active in skeletal muscle of people with breast cancer and lung cancer that had metastasised to bone, and that in this case too it caused muscle weakness in people with cancer.
When the researchers prevented calcium leakage using a small molecule known as 

which prevented the release of TGFβ from the bone. The researchers also used various other inhibitors of TGFβ which prevented TGFβ signalling in muscle and the increase in Nax1 protein. The researchers also prevented muscle weakness when they blocked Nax1 activity directly using a small molecule inhibitor.

A similar set of experiments was also done using mouse breast cancer cells in mice. This was done to see if the immune system of mice could be playing a role in muscle weakness, loss of muscle size, or growth of tumour cells in the bone. The work with human cancer cells required injection of the human cells into an immunodeficient mouse often referred to as nude mice since they lack fur. The researchers found the same results using mouse tumour cells as when they used human tumour cells in an immunodeficient mouse, suggesting that the immune system is not playing a large role in cancer-associated muscle weakness.

These studies have the potential to improve the quality of life and survival of cancer patients.