With muscle-building treatment, mice live longer even as tumors grow

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In the vast majority of patients with advanced cancer, their muscles will gradually waste away for reasons that have never been well understood. Now, researchers reporting in the August 20 issue of *Cell*, have found some new clues and a way to reverse that process in mice. What's more, animals with cancer that received the experimental treatment lived significantly longer, even as their tumors continued to grow.

"This is the first demonstration that muscle mass plays a key role in cancer survival," said H.Q. Han of Amgen Research.

While it has long been recognized that this muscle wasting condition, known as cachexia, affects advanced cancer patients' quality of life, Han explained, its importance for survival had primarily been a matter of speculation. Nearly 30 percent of cancer-related deaths have been attributed to cachexia, but that was based on correlative evidence only. That is, there has seemed to be a connection in cancer patients between weight loss and mortality.

Still, cachexia had typically been considered a "multi-factorial" process with many causes. "That would make it hard to target," Han said. Indeed, few therapeutic options are available and efforts to treat this aspect of the disease haven't been top of mind. Given the new results, that could change.

The researchers suspected that a pathway known as ActRIIB might be involved. ActRIIB is what's known as an activin type 2 receptor. There

was evidence to suggest that tumors secrete activin, such that circulating levels of the protein rise in those with cancer. Activin is closely related to another protein, called myostatin, which is known to be important in muscle. Animals lacking myostatin or taking treatments that block it grow bigger muscles. There was some evidence to suggest that activin blockers might have a similar effect.

Based on that hunch, the researchers treated mice with cancer and associated cachexia with a recombinant and soluble version of the ActRIIB receptor (sActRIIB), a kind of molecular "decoy" that potently inhibited both activin and myostatin activity. That treatment reversed the animals' muscle loss and prolonged their survival by several weeks on average. That was despite the fact that the tumors appeared to be unaffected. The animals also kept losing fat and still had high levels of inflammatory factors.

"In tumor-bearing mice with profound cachexia, blocking this pathway not only prevents muscle wasting but completely reverses the loss of muscle, strength and anorexia," Han said. (Anorexia is another symptom of cachexia, but appetite stimulants and nutritional supplements don't help much.)

The researchers also found something that had apparently gone unnoticed before. Just as the skeletal muscles of mice with cancer withered away, so too did their heart muscle. The ActRIIB inhibiting treatment completely reversed that too.

Han said that finding may point to an unappreciated role for heart atrophy in muscle wasting conditions more broadly.

Further experimentation showed that the ActRIIB blockade prevented muscle proteins from being marked for degradation and markedly stimulated muscle stem-cell growth. Muscle stem cells were successfully

activated even in muscle that had lost 50 percent of its weight prior to treatment, Han said.

"This is the first indication that there may be a major medical benefit in extending life span by combating cachexia," Han said, emphasizing however that there is a long way to go from preclinical studies in mice to clinical trials in human patients.

Still, he added, "as drug discovery scientists, we are very excited by the implications. This suggests a promising strategy for treating cachexia and underscores the need for further investigation and translational research to fully understand this pathway and explore the benefits of its antagonism."

The researchers say it will be important to explore levels of myostatin and other components of the ActRIIB pathway in various patient groups. "The dramatic, reversible changes in body mass shown here emphasize the importance of obtaining such information not only for understanding disease mechanisms but also to provide a fuller rationale for anti-activin therapies," they wrote. "However, since the inhibition of ActRIIB signaling by sActRIIB induces growth of normal muscle, this treatment is likely to be anabolic and help combat muscle loss in many catabolic conditions, even if the wasting is not triggered by excessive signaling by activin or related ligands of the ActRIIB pathway."

Han says he and his colleagues hope the findings will renew interest among cancer researchers and oncologists in cachexia. "Our results argue that blocking the catabolic actions of tumors should be a major therapeutic objective, not only to enhance quality of life but also to prolong survival," he said.

More information: Zhou et al.: “Reversal of Cancer Cachexia and Muscle Wasting by ActRIIB Antagonism Leads to Prolonged Survival.”

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