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Cancer wasting due in part to tumor factors that block muscle repair, study shows

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A new study reveals that tumors release factors into the bloodstream that inhibit the repair of damaged muscle fibers, and that this contributes to muscle loss during cancer wasting. The condition, also called cancer cachexia, accompanies certain types of cancer, causes life-threatening loss of body weight and lean muscle mass, and is responsible for up to one-in-four cancer deaths. There is no treatment for the condition.

The study was led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), and it points to new strategies and new drug targets for treating cancer cachexia.

The findings were published in the *Journal of Clinical Investigation*.

The researchers looked at muscle stem cells, which are also called satellite cells. These cells are associated with muscle fibers and are essential for repairing damaged fibers. Normally, damage to muscle fibers causes these stem cells to proliferate and to differentiate into mature muscle cells. These muscle cells then fuse with damaged surrounding fibers to limit muscle wasting. This process is blocked during cancer cachexia, the researchers say.

"Our study showed that although muscle stem cells are activated during cachexia, factors released by the tumor block these cells from differentiating into muscle cells, which leaves them unable to repair cachectic muscle fibers," says principal investigator Denis Guttridge,

PhD, professor of molecular virology, immunology and medical genetics and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

"By identifying agents that overcome the block and allow muscle stem cells to differentiate, it might be possible to restore muscle mass and enhance the quality of life of cancer patients with cachexia," he says.

For this study, Guttridge and his colleagues used animal models and tissue from cachectic pancreatic-cancer patients to identify factors in the muscle microenvironment that contribute to cancer cachexia. Key findings include:

- Cachexia is associated with tumor-induced damage to skeletal muscle cells and tumor-induced proliferation of muscle stem cells;
- Overexpression of the muscle stem cell factor, Pax7, blocks the cells' ability to differentiate and promotes cancer-induced wasting;
- The overexpression of Pax7 promotes cancer wasting by blocking the maturation of muscle cells and their fusion with surrounding fibers, which allows muscle to gain mass;
- The overexpression of Pax7 is controlled by NF-kappa B (NF-kB), which has been shown to play multiple roles in cancer. In cachexia, NF-kB causes the deregulation of Pax7 expression, which in turn impairs differentiation of muscle progenitor cells and promotes muscle atrophy;
- Because of its tissue specificity, Pax7 inhibition might offer an attractive therapy for cancer cachexia.

"For decades, studies in cachexia have focused on mechanisms that lead to muscle wasting from within skeletal muscle fibers," Guttridge says. "Our study is the first to show proof of concept that events occurring

outside the muscle fiber and within the muscle microenvironment also play a part in driving muscle wasting in cancer."

More information:
www.ncbi.nlm.nih.gov/pubmed/?term=10.1172/JCI68523

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