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Stem cell transplants in mice produce lifelong enhancement of muscle mass

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A University of Colorado at Boulder-led study shows that specific types of stem cells transplanted into the leg muscles of mice prevented the loss of muscle function and mass that normally occurs with aging, a finding with potential uses in treating humans with chronic, degenerative muscle diseases.

The experiments showed that when young host mice with limb muscle injuries were injected with muscle stem cells from young donor mice, the cells not only repaired the injury within days, they caused the treated muscle to double in mass and sustain itself through the lifetime of the transplanted mice. "This was a very exciting and unexpected result," said Professor Bradley Olwin of CU-Boulder's molecular, cellular and developmental biology department, the study's corresponding author.

Muscle stem cells are found within populations of "satellite" cells located between muscle fibers and surrounding connective tissue and are responsible for the repair and maintenance of skeletal muscles, said Olwin. The researchers transplanted between 10 and 50 stem cells along with attached myofibers -- which are individual skeletal muscle cells -- from the donor mice into the host mice.

"We found that the transplanted stem cells are permanently altered and reduce the aging of the transplanted muscle, maintaining strength and mass," said Olwin.

A paper on the subject was published in the Nov. 10 issue of Science

Translational Medicine. Co-authors on the study included former CU-Boulder postdoctoral fellow John K. Hall, now at the University of Washington Medical School in Seattle, as well as Glen Banks and Jeffrey Chamberlain of the University of Washington Medical School.

Olwin said the new findings, while intriguing, are only the first in discovering how such research might someday be applicable to human health. "With further research we may one day be able to greatly resist the loss of muscle mass, size and strength in humans that accompanies aging, as well as chronic degenerative diseases like muscular dystrophy."

Stem cells are distinguished by their ability to renew themselves through cell division and differentiate into specialized cell types. In healthy skeletal muscle tissue, the population of satellite stem cells is constantly maintained, said Olwin.

"In this study, the hallmarks we see with the aging of muscles just weren't occurring," said Olwin. "The transplanted material seemed to kick the stem cells to a high gear for self-renewal, essentially taking over the production of muscle cells. But the team found that when transplanted stem cells and associated myofibers were injected to healthy mouse limb muscles, there was no discernable evidence for muscle mass growth.

"The environment that the stem cells are injected into is very important, because when it tells the cells there is an injury, they respond in a unique way," he said. "We don't yet know why the cells we transplanted are not responding to the environment around them in the way that the cells that are already there respond. It's fascinating, and something we need to understand."

At the onset of the experiments the research team thought the increase in muscle mass of the transplanted mice with injured legs would dissipate

within a few months. Instead, the cells underwent a 50 percent increase in mass and a 170 percent increase in size and remained elevated through the lifetime of the mice -- roughly two years, said Olwin.

In the experiments, stem cells and myofibers were removed from three-month-old mice, briefly cultured and then transplanted into three-month-old mice that had temporarily induced leg muscle injuries produced by barium chloride injections. "When the muscles were examined two years later, we found the procedure permanently changed the transplanted cells, making them resistant to the aging process in the muscle," he said.

"This suggests a tremendous expansion of those stem cells after transplantation," Olwin said. Fortunately, the research team saw no increase in tumors in the transplanted mice despite the rapid, increased growth and production of muscle stem cells.

As part of the research effort, the team used green fluorescent protein -- which glows under ultraviolet light -- to flag donor cells in the injected mice. The experiment indicated many of the transplanted cells were repeatedly fused to myofibers, and that there was a large increase in the number of satellite cells in the host mice.

"We expected the cells to go in, repopulate and repair damaged muscle and to dissipate," Olwin said. "It was quite surprising when they did not.

"It is our hope that we can someday identify small molecules or combinations of small molecules that could be applied to endogenous muscle stem cells of humans to mimic the behavior of transplanted cells," Olwin said. "This would remove the need for cell transplants altogether, reducing the risk and complexity of treatments."

But Olwin said it is important to remember that the team did not transplant young cells into old muscles, but rather transplanted young

cells into young muscles.

The research has implications for a number of human diseases, Olwin said. In muscular dystrophy, for example, there is a loss of a protein called dystrophin that causes the muscle to literally tear itself apart and cannot be repaired without cell-based intervention. Although injected cells will repair the muscle fibers, maintaining the muscle fibers requires additional cell injections, he said.

"Progressive muscle loss occurs in a number of neuromuscular diseases and in muscular dystrophies," he said. "Augmenting a patient's muscle regenerative process could have a significant impact on aging and diseases, improving the quality of life and possibly improving mobility."

Olwin said the research team is beginning experiments to see if transplanting muscle stem cells from humans or large animals into mice will have the same effects as those observed in the recent mouse experiments. "If those experiments produce positive results, it would suggest that transplanting human muscle stem cells is feasible," he said.

Provided by University of Colorado at Boulder