Researchers solve key part of old mystery in generating muscle mass

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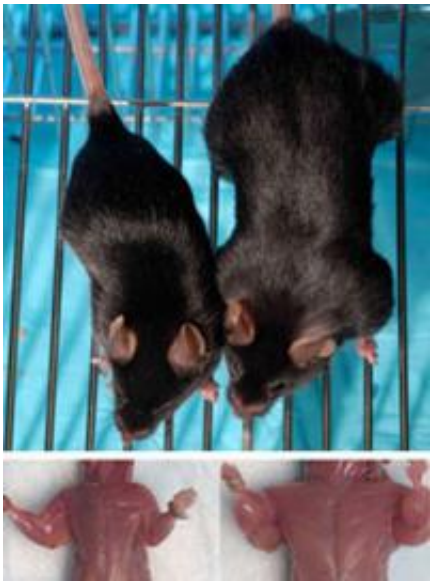

Mice without the gene for myostatin (right) have nearly twice as much muscle mass as normal mice (left). Credit: Se-Jin Lee Lab

Working with mice, Johns Hopkins researchers have solved a key part of a muscle regeneration mystery plaguing scientists for years, adding strong support to the theory that muscle mass can be built without a complete, fully functional supply of muscle stem cells.

"This is good news for those with muscular dystrophy and other muscle wasting disorders that involve diminished stem cell function," says Se-Jin Lee, M.D., Ph.D., lead author of a report on the research in the

August issue of the Proceedings of the National Academy of Sciences, and professor of molecular biology and genetics at the Johns Hopkins University School of Medicine.

Muscle stem cells, known as satellite cells, reside next to muscle fibers and are usually dormant in adult mammals, including humans. After exercise or injury, they are stimulated to divide and fuse, either with themselves or with nearby muscle fibers, to increase or replace muscle mass. In muscle wasting disorders, like muscular dystrophy, muscle degeneration initially activates satellite cells to regenerate lost tissue, but eventually the renewal cycle is exhausted and the balance tips in favor of degeneration, the researchers explain.

Muscle maintenance and growth under healthy, non-injury conditions have been more of a mystery, including the role of myostatin, a protein secreted from muscle cells to stop muscle growth. Blocking myostatin function in normal mice causes them to bulk up by 25 to 50 percent. What is not known is which cells receive and react to the myostatin signal. Current suspects include satellite cells and muscle cells themselves.

In this latest study, researchers used three approaches to figure out whether satellite cells are required for myostatin activity. They first looked at specially bred mice with severe defects in either satellite cell function or number. When they used drugs or genetic engineering to block myostatin function in both types of mice, muscle mass still increased significantly compared to that seen in mice with normal satellite cell function, suggesting that myostatin is able to act, at least partially, without full satellite cell function.

Second, the researchers guessed that if myostatin directly inhibits the growth of satellite cells, their numbers should increase in the absence of myostatin. The researchers marked the satellite cells with a permanent

dye and then blocked myostatin activity with a drug. Mouse muscle mass increased significantly as expected, but the satellite cells did not increase in number, nor were they found fusing with muscle fibers at a higher rate. According to Lee, these results strongly suggest that myostatin does not suppress satellite cell proliferation.

Third, to further confirm their theory that myostatin acts primarily through muscle cells and not satellite cells, the team engineered mice with muscle cells lacking a protein receptor that binds to myostatin. If satellite cells harbor most of the myostatin receptors, removal of receptors in muscle cells should not alter myostatin activity, and should result in muscles of normal girth. Instead, what the researchers saw was a moderate, but statistically significant, increase in muscle mass. The evidence once again, they said, suggested that muscle cells are themselves important receivers of myostatin signals.

Lee notes that, since the results give no evidence that satellite cells are of primary importance to the myostatin pathway, even patients with low muscle mass due to compromised satellite cell function may be able to rebuild some of their muscle tone through drug therapy that blocks myostatin activity.

"Everybody loses muscle mass as they age, and the most popular explanation is that this occurs as a result of satellite cell loss. If you block the myostatin pathway, can you increase muscle mass, mobility and independence for our aging population?" asks Lee. "Our results in mice suggest that, indeed, this strategy may be a way to get around the satellite cell problem."

More information: www.pnas.org/content/109/35/E2353.full

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