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Tumor suppressor key in maintaining stem cell status in muscle

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A gene known to suppress tumor formation in a broad range of tissues plays a key role in keeping stem cells in muscles dormant until needed, a finding that may have implications for both human health and animal production, according to a Purdue University study.

Shihuan Kuang, professor of animal sciences, and Feng Yue, a postdoctoral researcher in Kuang's lab, reported their findings in two papers published in the journals *Cell Reports* and *Nature Communications*. The results suggest modifying expression of the PTEN gene could one day play a role in increasing muscle mass in agricultural animals and improve therapies for muscle injuries in humans.

Muscle stem cells, called satellite cells, normally sit in a quiescent, or dormant, state until called upon to build muscle or repair a damaged muscle. Inability to maintain the quiescence would lead to a loss of satellite cells. As humans age, the number of satellite cells gradually declines and the remaining cells become less effective in regenerating muscles, resulting in muscle loss – a condition called sarcopenia.

Kuang and Yue, in the *Nature Communications* paper, explored the role tumor-suppressor gene PTEN plays in satellite cells. The PTEN gene encodes a protein that suppresses the growth signaling, thereby, limiting the growth of fast-growing tumor cells. Mutation of the PTEN gene is associated with many types of cancers, but how the gene functions in muscle stem cells is unknown.

To understand the function of a gene, the authors first wanted to know how the gene is expressed.

"This gene is highly expressed in the satellite cells when the cells are in the quiescent state. When they become differentiated, the PTEN level reduces," Yue said.

By knocking out the PTEN gene in resting satellite cells, the researchers found that satellite cells quickly differentiate and become muscle cells. So PTEN plays an essential role in keeping satellite cells in their quiescent state.

"You no longer have the stem cells once you knock out the gene," Kuang said.

In their *Cell Reports* paper, Kuang and Yue took a step further to examine PTEN function in proliferating stem cells. This time, they knocked out PTEN in embryonic progenitor cells, those that will later become muscle in the mouse. They found that as the mouse grew, muscle mass increased significantly—by as much as 40 percent in some muscles—over that of a normal mouse.

"That would be significant in an animal production point of view," Kuang said.

The increased muscle came with a cost, however. Besides creating muscle, those progenitor cells create satellite cells. Without PTEN, not only fewer satellite cells were created, but the resulting satellite cells cannot maintain dormancy, leading to an accelerated rate of depletion during aging.

The faster depletion of satellite cells during aging wouldn't matter much in an animal production scenario, Kuang said. Beef cattle, for example,

are harvested before they age. The increase in muscle mass, however, would be a significant advantage in production efficiency.

The findings may lead to improvement in human health, the authors said. The ability to control the expression of PTEN could lead to therapies for quicker healing of muscle injuries.

"If you want to quickly boost up the stem cells to repair something, you need to suppress PTEN," Kuang said. "After that, you'd need to increase PTEN to return the cells back to quiescent state. If we could do that, you would suspect that the muscle would repair more quickly."

Knowing that PTEN also suppresses tumors in many types of tissues, the authors noted that the elimination of the gene did not cause tumor formation in the muscle cells they studied. That suggests regulation of PTEN could be a feasible method for improving human health and animal agriculture.

More information: Feng Yue et al. Pten is necessary for the quiescence and maintenance of adult muscle stem cells, *Nature Communications* (2017). DOI: 10.1038/ncomms14328

Feng Yue et al. Conditional Loss of Pten in Myogenic Progenitors Leads to Postnatal Skeletal Muscle Hypertrophy but Age-Dependent Exhaustion of Satellite Cells, *Cell Reports* (2016). DOI: 10.1016/j.celrep.2016.11.002

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