Mightier Mice Are on the Way

Genetic Altering Increases Muscle, Not Fat

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Scientists tinkering with a newly discovered gene have created a strapping breed of mouse with muscles that are two to three times bigger than those of normal mice.

The mighty mice may help researchers find treatments for muscular dystrophy, the scientists said, or for the gradual muscle wasting that accompanies cancer or AIDS. The mice may also shed light on the mechanisms by which exercise increases muscle mass, and perhaps speed development of a drug that builds bigger muscles without trips to the gym.

More immediately, experts said, the work may facilitate the creation of genetically engineered farm animals with double the standard amount of meat. The brawny rodents have no more fat than their scrawny counterparts, suggesting that farm animals bearing the same genetic trait would offer larger yet leaner cuts than are available now.

"They do look a little strange," said Alexandra McPherron, who engineered the muscle-bound mice with Se-Jin Lee and Ann M. Lawler, all of Johns Hopkins University. "The shoulders and hips look a little bulky, and the way they move is a little sluggish."

But the mice are otherwise perfectly healthy, McPherron said, and have proved fertile in matings with their own muscular breed -- producing muscular offspring -- and with normal mice.

Other researchers praised the work but cautioned that any number of difficulties could prevent the new finding from making its way to medical clinics or Olympic training centers.

It is not clear, for example, whether the equivalent gene in humans -- already found by the Hopkins team -- behaves the same way in people as the mouse gene does in mice. Nor has anyone found a way to turn the gene on or off in adults; the muscular mice were born with the gene already flipped to the "make more muscle" mode, and no drug yet exists that can accomplish that after an animal is born.

Moreover, it is still not clear that the muscular mice are actually stronger than normal mice. Those tests are now underway.

"I think its potential is going to be very urgently applied to animal husbandry, but application to people will be a little more difficult," said Leon Charash, chairman of the medical advisory board for the Muscular Dystrophy Association.

The gene was one of several that McPherron and her colleagues recently found as part of a search for genes that help cells grow and communicate with each other. She and Lee are affiliated with Baltimore-based MetaMorphix Inc., a company that hopes to develop therapies for muscle wasting diseases, and the new gene caught their eye because it seems to operate only in muscle cells.

To see what the gene does in those muscle cells, the team knocked out the gene in some mouse embryo cells, then allowed the embryos to develop into mice. The result was the burly breed of rodent they describe in today's issue of the journal Nature.

Further work showed that the gene makes a protein (the team has dubbed it myostatin) that normally keeps muscle growth in check. When that regulatory gene is absent, mice grow bigger muscles.

Only striated muscle is affected -- not heart muscle or the muscle that makes up the digestive tract -- with most of the added bulk appearing in the shoulders, face, legs, chest and abdomen. The extra mass is due to an increase in both the number and size of muscle fibers within each muscle. That suggests myostatin may

have potential as a treatment for muscle cancers, scientists said, since those cancers involve an overgrowth of muscle fibers.

No one knows whether myostatin would have to be missing from conception for a person to develop larger muscles, or whether a drug that blocks myostatin's action in adults might release a new round of muscle growth in bodybuilders or people with muscle diseases.

In farm animals, however, it might not be hard to develop a line of myostatin-free animals. "In agriculture, the idea would be to try to delete this gene from chickens, cows, pigs or whatever," Lee said. "And the question is, `Would we then have an animal with two to three times the muscle mass that current animals have?' "

"It's very interesting and very exciting, and indeed the projected possibilities are sound," said Joan Massague, a researcher at Memorial Sloan-Kettering Cancer Center in New York who in the 1980s conducted pioneering work on the family of signaling compounds to which myostatin belongs. "The question I would have about this new member of the family is whether, when used as a drug, it will concentrate in the muscle and only in the muscle. Or whether, once presented, it would act on other cells too, which might not be desirable."

Dan Laster, director of the Agriculture Department's meat animal research center in Clay Center, Neb., said standard breeding and selection techniques have already led to the development of "double muscled cattle" and "heavy muscled lambs," but some of those breeds "have some problems with eating quality," such as toughness.

"We, and I'm sure others, will look at this gene," Laster said, to see if it can lead to the development of more and tastier meat.

And perhaps more mellow farm animals, too. The Hopkins mice, it turns out, are gentle giants, less likely to react when poked and prodded than are normal mice. "Actually," McPherron said at a news media preview of the mice yesterday, "the normal one there is beating up the big muscular one."
[Illustration]

PHOTO,,Keith Weller CAPTION: Johns Hopkins University scientists Se-Jin Lee and Alexandra McPherron compare regular mouse with brawny strain, at right. CAPTION: Genetically engineered mice such as the one at left, bred at Johns Hopkins University School of Medicine, have broad hips and shoulders and move more sluggishly than ordinary strains but are otherwise healthy, according to scientists. The muscular mice have proved fertile in matings with their own breed -- producing muscular offspring -- and with normal mice.

Credit: Washington Post Staff Writer