Science File

'Mighty Mouse' Gene Identified

Muscle-producing protein could be manipulated to treat muscular diseases and create meatier livestock.

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Discerning readers might spot a difference between the two mice pictured on this page: One of them is really big.

The big one isn't fat--it's muscle-bound. But the mouse hasn't been putting in overtime on the exercise wheel or nibbling away on chow laced with anabolic steroids.

Instead, the difference between the slim, svelte mouse and the big, brute mouse stems from a single gene--one that plays a key role in the growth and development of muscle.

"It's quite a sight," says Se-Jin Lee, molecular biologist at Johns Hopkins University, of this and other "mighty mice" his lab has produced.

The brute mice are impressive, Lee says, even when their muscles are hidden under fur. And when the muscle is directly viewed, the contrast is just plain dramatic. In the engineered mice, the leg muscles and chest muscles are hugely--grotesquely--inflated, up to four times larger than those of normal animals.

Such mice look grotesque, but Lee hopes that the principle they illustrate will lead to useful and important things. If researchers can develop drugs that would affect the body the way the gene--or its absence--does, farmers could grow meatier pigs and poultry. And doctors might have medicines to treat muscle-wasting human diseases like the muscular dystrophies.

For diseases, "the idea is to increase muscle mass, significantly improve quality of life and extend life," Lee says, by tapping into the natural genetic processes that form our skeletal muscle to begin with.

Muscle gets its start from blocks of cells called somites distributed in stripes down the length of the young embryo. As the embryo develops, cells start creeping out from the somites toward different sites in the developing body, to eventually form biceps, triceps, back muscles, and more. An array of genes is involved in directing the journey and transformation of fairly unspecialized cells into long, stripy fibers that we can contract and relax on demand. Lee stumbled on one of those genes quite by chance.

He and his lab team were examining a medley of genes to figure out the role each played in the making of a mouse. Their method was simple--first they would use a genetic trick to create mice in which a specific gene was destroyed. Then they would closely examine the mice and note what, if any, part of their development was abnormal.

He's Not Fat, He's Big-Muscled

The results of the study were many strange mice, but one kind really stood out because of its sheer muscular bulk. Clearly, the gene that had been turned off in that particular line was involved in deciding how big a creature's muscles should be--and putting a brake on too much growth. That brake was removed when Lee destroyed the gene. Mice with super-bulky muscles were the result.

The mice are no fatter than before, and have normal heart and gut muscles. Only skeletal muscles (which we control voluntarily to breathe and move our body) are enlarged. The muscles have both extra fibers and larger ones. And the extra muscles appear to be doing something.

"Even from just holding an animal's tail and letting it grip onto the cage you can get a pretty good idea of an animal's strength-- and it's pretty clear these animals are much stronger," Lee says.

Lee reported his first "mighty mice" in 1997, in an article in the scientific journal Nature. He christened the gene "myostatin."

Since then, he has continued to experiment, and earlier this year reported more mighty mice created by altering other genes, such as one called follastatin, that are linked to the action of myostatin. (The paper was published in the Proceedings of the National Academy of Sciences in July.)

No one knows exactly what the growth genes do. Researchers do know the myostatin gene is active in the developing muscle all the way from the embryo to the fully formed muscle of an adult. They also know the myostatin gene directs the formation of a protein that is presumed to bind in the surface of muscle fibers. By binding, the myostatin protein probably instructs cells to stop growing so much.

To Lee, the discovery of the myostatin pathway is exciting because it provides a clue to a question that has long fascinated him: how various parts of the body know how large they should grow.

The liver is particularly remarkable in this capacity, he says: When part of it is removed, what's left behind will grow until it reaches its original size--and then stop.

Decades ago, scientists proposed that small chemicals released by the liver or other body parts might provide feedback clues that help to govern size. (The larger the liver, for instance, the more of the chemical it would make.) If that theory is correct--and Lee suspects it is--myostatin is a prime candidate for creating a chemical that keeps muscles at a certain size, he says.

Lee also speculates that somehow the actions of exercise and anabolic steroids might feed into the myostatin pathway and tip the balance toward more muscle.

Lee is also excited about the myostatin muscle control pathway for more practical, down-to-earth reasons: the possibilities it suggests for new drugs.

Two companies have licensed the patented technology from Johns Hopkins University--one to develop new products for agriculture, the other to apply myostatin's lessons to medicine.

In agriculture, the idea is to develop drugs that interfere with myostatin so as to make meatier swine and poultry, says Edwin Quattlebaum, chair and chief executive officer of the Baltimore-based company MetaMorphix Inc. Lee is one of the company's stockholders. In early trials, injecting a small protein that inhibits myostatin into chicken eggs resulted in up to a 21% increase in live weight of the chicks, he says.

Drugs Could Be Used for AIDS, Dystrophies

The company is also doing trials with pigs and working with vaccines that could cajole the animal's immune system to destroy myostatin.

"We're very excited," Quattlebaum says. "Clearly we have a long way to go but the potential is enormous."

Such drugs might also increase the meatiness of cattle--in fact, some livestock breeders unwittingly already have selected animals with altered myostatin. Bulky Belgian Blue and buff Piedmontese cattle both have huge, well-defined musculatures known as the "double muscling" trait. Lee and others have shown that both breeds have inactive or less active myostatin genes.

Meanwhile, American Home Products, the large pharmaceutical company based in Madison, N.J., is trying to develop drugs that inhibit the myostatin pathway in order to treat human diseases.

Such a drug might be used to help combat the muscle-wasting often seen in patients with AIDS or cancer--and perhaps even the loss of muscle mass that comes with age, says Steve Clark, senior vice president of discovery research at Wyeth-Ayerst, the pharmaceutical arm of American Home Products. Retaining extra muscle padding might lower the risk of fractures when an elderly person falls, Clark says.

Muscle-building drugs also could treat people with muscular dystrophies, an array of related conditions where muscles are abnormal and get repeatedly damaged, leading eventually to lack of muscle function and premature death.

There is currently no effective treatment for muscular dystrophy, says Louis Kunkel, professor of pediatrics and genetics at Harvard Medical School. He sees the myostatin approach as one of several promising research directions aimed at filling that gap.

"Clearly, if you could tweak the myostatin pathway, it might increase muscle bulk, which could potentially increase muscle strength and slow progression of the disease," he says. "However," he cautions, "there is no evidence right now to show that it would actually work."

Indeed, it's not yet clear if any of these myostatin dreams will come to fruition, says Lee. A lot depends on whether the myostatin pathway continues to affect muscle size after embryonic development and birth. If not, you could give a creature all the drugs you want, and the muscles wouldn't alter their size.

An adult effect seems likely, Lee says, but hasn't yet been definitively shown.

If the concept does work, cattle ranchers and doctors won't be the only people interested in the drugs. There is definitely the potential for abuse among those who would like to develop bigger, buffer bodies without the side effects of anabolic steroids.

"Ultimately anything that could be applied to patients with wasting conditions would almost certainly lead to abuse problems," says Lee. "But the potential for good is extraordinary."
[Illustration]
Caption: PHOTO: A normal mouse, left, is compared to a mouse with a mutant myostatin gene. The big one isn't fat--it's muscle-bound. "It's pretty clear these animals are much stronger," Dr. Se-Jin Lee says.; PHOTOGRAPHER: KEITH WELLER / JHMI; PHOTO: Some livestock breeders unwittingly already have selected animals with

altered myostatin, such as this bulky Belgian Blue bull.; PHOTOGRAPHER: National Academy of Sciences

Credit: TIMES MEDICAL WRITER