NATIONAL DESK

A Lab Breeds a Mighty Mouse, With a Variety of Implications

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A new breed of mice with more than twice the normal amount of muscle may lead to meatier chickens and cows and, eventually, new treatments for people with muscle diseases, researchers are reporting.

The mice, described today in the journal Nature, owe their bulging physiques to the lack of a gene that would normally limit muscle growth. The function of the gene was previously unknown, and its discovery, by a team led by Dr. Se-Jin Lee of Johns Hopkins University, is considered an important advance.

"It has opened up completely new ideas about the control and regulation of muscle growth," said Dr. Brigid Hogan, a professor of cell biology at Vanderbilt University.

Another researcher who was not involved in the study, Dr. Lee Niswander of the Memorial Sloan-Kettering Cancer Center in Manhattan, said: "Until now, we didn't have a clue about what told muscle cells to stop dividing. This gives us a handle on understanding it. It's powerful."

Dr. Lee and his colleagues actually found the gene in 1992 but did not know then what it did. Within a year or so, they had determined that it was active in muscle but still did not know just what role it played.

To find out, they began developing a strain of mice in which the newly found gene was "knocked out," or deleted, a standard research technique. Abnormalities in the knockout mice were then studied for clues to the function of the missing gene.

The first knockouts were born last year and by about six weeks of age had developed an odd body shape, with unusually big shoulders and hips. When these mice were examined after death, the bulges turned out to be muscle: the skeletal muscles were two to three times the size of those in normal mice. (No other types of muscle, like cardiac muscle or the smooth muscle of the intestines, were affected.)

The researchers were surprised.

"We thought maybe the mice wouldn't have any muscle at all," said Alexandra McPherron, a Johns Hopkins graduate student who was the lead author of the Nature paper. "We certainly didn't expect they'd have more muscle."

The gene being studied -- myostatin, or growth/differentiation factor 8 -- is the newest known member of a family of genes, now numbering about 30, that regulate cell growth and organ development.

"We got interested in the family because a number of the factors in it showed enormous promise in terms of clinical applications," Dr. Lee said.

The family is known as transforming growth factor-beta genes. Members that Dr. Lee cited as examples included bone morphogenetic proteins, which are being tested in people as an aid to fracture healing, and a substance known as a

neurotrophic factor that may prove to have a role in treating Parkinson's disease and Lou Gehrig's disease.

Dr. Lee said the most immediate application of the myostatin findings might be to agriculture. Chickens, cows and pigs all have the gene, and he said that if it works in them as it does in mice, knockouts might produce twice as much meat with no more fat.

Humans also have the gene, and Dr. Lee said he hoped the research might ultimately lead to new treatments for diseases like muscular dystrophy and for the severe muscle wasting that causes disability and premature death in some people with cancer and AIDS.

"But that's a long way off," he added, "years away."

One concern is that turning off the myostatin gene might cause cancer. Other genes in its family are tumor suppressors, and when they are removed or blocked, the animals die of cancer. The new mice are being watched for this, Dr. Lee said.

So far, with some of the animals over a year old -- about half the life span of a mouse -- no tumors have been found. Except for their big muscles, the mice appear physically normal, the researchers said.

But they do behave differently from ordinary mice. Ms. McPherron, who was bitten by one of the animals at the news conference announcing their debut, nonetheless described them as gentler than normal mice, and "a little sluggish."

"A normal mouse runs away when you poke it," Ms. McPherron said. "These only move a little."

The researchers do not know why, she said.

"I'm guessing," she said. "When I look at bodybuilders, I think they probably can't run very fast, can't drag all that muscle around."

But when the mice finally do move, she added, they move normally. Asked if they might be less fearful, or less intelligent, than normal mice, she said: "Big and stupid? We don't know. Maybe they don't understand that when somebody pokes you, you should get out of the way. Or maybe the gene affects aggression."