Building Bigger Mice Through Gene Transfer

Mice that acquire a transferred gene for rat growth hormone make excess quantities of the hormone and grow larger than normal

Within the past year the extraordinary has become commonplace. New genes can be reliably introduced into the germ lines of experimental animals, including fruit flies and mice, and transmitted to their progeny. But getting the transferred genes expressed efficiently has been more difficult, especially in mice.

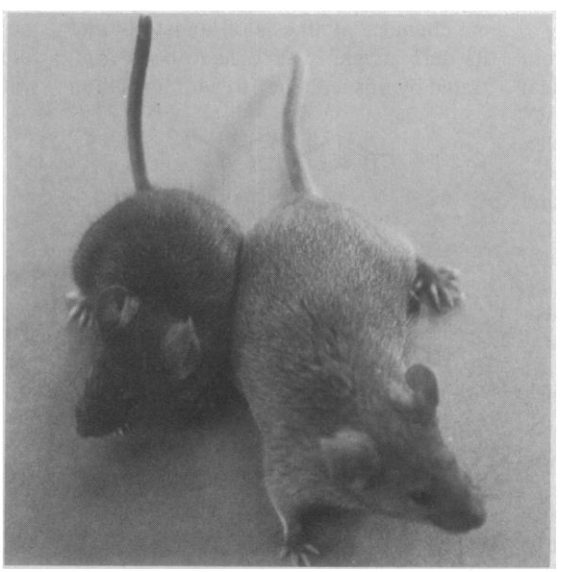
Now, investigators from the laboratories of Richard Palmiter at the Howard Hughes Medical Institute of the University of Washington, Ralph Brinster of the School of Veterinary Medicine of the University of Pennsylvania, and Ronald Evans of the Salk Institute have shown that a foreign gene introduced into mice directs the synthesis of large quantities of its product, growth hormone.* Just as important, the mice respond to the hormone—they grow almost twice as big as animals that do not carry the foreign gene. The gene transfer method might be used, the investigators propose, to develop new breeds of rapidly growing domestic animals, to either mimic or correct genetic diseases, and to produce commercial quantities of important proteins in farm animals. However, the investigators' primary goal is to use gene transfer to study gene expression during development.

The rat gene to be transferred into mice was first modified by replacement of the regulatory sequences on its 5′ terminal—that is, the end of the gene where transcription into messenger RNA begins—with a corresponding region from the mouse metallothionein (MT) gene. This sequence contains the MT promoter, which helps to control expression of the gene. The investigators then injected about 600 copies of the fusion gene into each of 170 newly fertilized mouse eggs, which were implanted into foster mothers. Brinster says, "We were optimistic that this particular experiment would work."

In previous experiments, Brinster and Palmiter had introduced into mice an analogous fusion gene, in which the MT promoter was attached to a viral gene. The viral protein was made in large quantities in about half of the animals carrying this hybrid gene, especially when the mice were fed low doses of zinc, a metal that normally increases MT gene expression.

In the current experiment, 21 mice developed from injected eggs. Seven of them carried one or more intact copies of the transferred growth hormone gene with its MT promoter.

After the mice were weaned, they were given a diet containing sufficient zinc to activate the MT promoter without impairing the animals' ability to breed. Six of the seven mice carrying the transferred gene grew significantly faster than littermates that did not acquire the gene. The animals with the largest number of gene copies, 10 to 35 per cell, grew the fastest and weighed from 70 to 80 percent more than control littermates when they were 74 days old.



Ralph Brinster

The new mighty mouse?

The mouse on the right, which weighs 41.2 grams, carries a transferred rat gene coding for growth hormone. Its normal littermate, which did not acquire the gene, weighs 21.2 grams. Both mice are about 10 weeks old.

The livers of the most rapidly growing mice contained substantially more copies of messenger RNA for the transferred gene than did livers of the slower-growing animals. Moreover, the growth hormone concentrations in serums from the fast-growing animals were also high—up to 800 times greater than usual.

"What really makes the experiment work," Brinster explains, "is the fusion gene. The MT promoter is a strong promoter. It is on constitutively in a number of tissues, including the liver. I think you could hook a lot of genes to the MT promoter and get expression."

Although the success of these experiments implies that similar methods might be used for such genetic engineering applications as the correction of inherited diseases in humans, Brinster notes that, in addition to the moral and ethical problems such applications would raise, there are substantial technical problems. One is the low survival of injected eggs, which is 10 percent or less.

Moreover, the pattern of expression of the transferred fusion gene is quite different from that of the normal growth hormone gene. The fusion gene is expressed to a high degree in liver, and possibly in other tissues, whereas the pituitary gland is the normal site of growth hormone synthesis.

The production of very high concentrations of growth hormone in some animals also suggests that the feedback mechanisms that would ordinarily turn off the growth hormone gene in the pituitary are not operating in the liver, which is perhaps not surprising. The outsized mice thus produced might be useful as models of gigantism, a genetic disease of humans caused by excess growth hormone, Brinster says, but "We are still a long way from controlling the gene."

Palmiter, Brinster, and Evans suggest that it may be possible to use their gene transfer method to develop rapidly growing strains of domestic animals, including pigs, cows, and sheep, although it remains to be seen if this will improve meat or milk production. It might also be possible to use the domestic animals to produce large quantities of important proteins, especially those that require additional processing after synthesis that might not be carried out by bacteria.

The transferred gene can be incorporated into the germ line and transmitted to future generations, a prerequisite for the agricultural applications. The fusion gene was inherited by 10 of the 19 offspring of one mouse. "We know the gene is transmitted," Brinster says, "and we know we get big mice in the second generation."—**JEAN L. MARX**

*The report by R. D. Palmiter, R. L. Brinster, R. E. Hammer, M. E. Trumbauer, M. G. Rosenfeld, N. C. Birnberg, and R. M. Evans appears in the 16 December issue of *Nature (London)*.

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