imprinted genes are known, and in two-thirds of them, the father contributes the active gene.

But the team found that *callipyge* adds yet another twist: Lambs that receive two copies of the mutated gene, one from each parent, look perfectly normal—a startling result. "You would not expect the homozygous animal not to express the trait," says Georges. He and Cockett first wondered whether the mutation was somehow corrected in the normal-looking offspring. But they ruled out that possibility by allowing homozygous males to mate with normal females—and seeing the buttocks of the heterozygous progeny balloon.

Geneticists have found other so-called overdominant genes, which are most strongly expressed in individuals with only one copy of the gene, and they are studying why these genes act this way. But there's only one other known case of an overdominant gene that also seems to show imprinting: a lethal mutation in mice, called *ovum*, which was described by geneticist Carmen Sapienza at Temple University Medical School in Philadelphia. "To my knowledge [*callipyge* and *ovum*] are the only two examples where there's both a parent of origin and genotype effect," says Sapienza.

Such rare genes offer insight into a whole class of non-Mendelian inheritance patterns that may have relevance for human diseases, says Chakravarti. For example, understanding the mechanism behind such patterns may explain the variability seen in Hirschsprung's disease, a genetic disorder of the digestive system. Not everyone with a mutant gene gets the disorder, and women appear to be less likely than men to show symptoms.

Georges and colleagues are still trying to figure out the details of what controls the expression of *callipyge*. But now that the gene's pattern of inheritance is known, sheep breeders can at least predict which matings will yield the biggest lamb chops.

**–Elizabeth Pennisi**

DEVELOPMENTAL BIOLOGY

# Synapse-Making Molecules Revealed

Every bend of the knee or blink of the eye depends on biochemical conversations between motor neurons and muscle cells. The lingua franca of these chats is the neurotransmitter, and during an embryo's development, the two kinds of cells must devise an intricate molecular junction, or synapse, to transfer these chemical signals. Now, with the help of two "conversationally impaired" mice, researchers have identified molecules from both muscle and nerve cells that lay the groundwork for these vital talks.

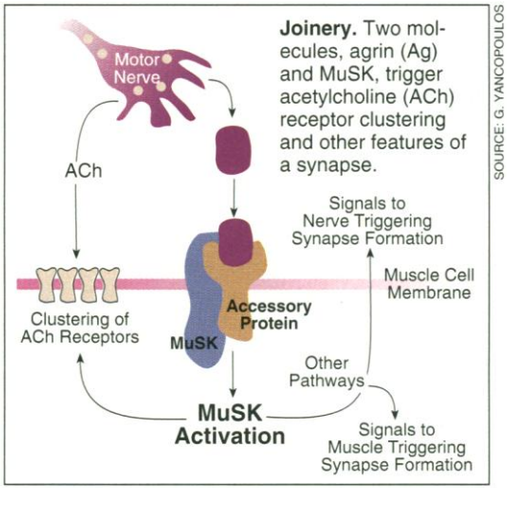
In the 17 May issue of *Cell*, a team of biologists describes "knockout" mice that are missing the gene for agrin, a nerve-derived protein, and are virtually devoid of neuromuscular junctions. Another team reports on a second set of knockout mice that can't make these connections—they lack the gene for a newly identified muscle protein named MuSK (for muscle-specific kinase). MuSK, it appears, is the agrin receptor: A third paper in the same issue shows that the two proteins bind and could spark a cascade of events that lead to the making of a synapse. "Together, the studies suggest that the agrin-MuSK interaction is the critical trigger [for synapse formation] without which you get absolutely nothing," says biologist George Yancopoulos of Regeneron Pharmaceuticals in Tarrytown, New York, who led the team that developed the MuSK knockouts.

Zach Hall, director of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, says the work "is a major step forward in understanding the signals passed between nerve and muscle to form the synaptic apparatus." Moreover, he notes, these signals might yield clues to junction formation in the brain itself, where agrin is abundant.

The building of a synapse involves clustering neurotransmitter receptors on the muscle cell, huddling of tiny vesicles at the nerve terminal, and expression of various structural proteins. Agrin has been a leading candidate for a synapse architect since the mid-1980s, when Jack McMahan's team at Stanford University isolated the protein and found that in muscle cells it drove the clustering of receptors for acetylcholine, the neurotransmitter that causes muscle contraction. The team had no idea how it drove this clustering, however, and because the work was done in tissue culture, no one could be sure that agrin did the same job in animals.

Joshua Sanes, who had worked with McMahan, followed up the agrin lead at Washington University in St. Louis. Together with Medha Gautam and Peter Noakes, he developed a strain of agrin-deficient mice. These animals were stillborn, and an autopsy revealed they showed almost no signs of neuromuscular junction formation, indicating that the protein indeed played a crucial role.

It takes two sides to form a junction, however, and Sanes's work still left open the identity of agrin's target—its receptor—on the muscle cell. The Regeneron researchers came upon it via a roundabout route. They had identified and cloned MuSK, an enzyme, and were looking into its role in muscle cell growth. Then they noticed that MuSK was expressed only at the neuromuscular junction. That made them wonder whether MuSK could be the agrin receptor.




**Joinery.** Two molecules, agrin (Ag) and MuSK, trigger acetylcholine (ACh) receptor clustering and other features of a synapse.

SOURCE: G. YANCOPOULOS

To test that idea, Thomas DeChiara of Regeneron created mice with defects in the MuSK gene and analyzed them in collaboration with Steven Burden's group at New York University Medical School. The rodents' nervous systems developed normally, but only up to a point: Neurons found their way to various muscles, but never sprouted synapses. "It was a spectacular phenotype," Yancopoulos recalls. "The mice had muscle but didn't use it. They never took their first breath of life."

Then the Regeneron team put agrin and MuSK together. Regeneron's David Glass and colleagues found that the two proteins bound very quickly, but only when MuSK was expressed in muscle cells. This suggested that MuSK was an agrin receptor, but also that an accessory muscle-specific protein, still unidentified, was needed to cement the connection. Once the link was made, MuSK became quite active, adding phosphate groups to acetylcholine receptors, for instance. The researchers theorize that this sets off a chain of chemical events—in both nerve and muscle cells—that ultimately constructs the molecular parts of the synapse.

Now the search is on for the identity of that accessory protein linking agrin to MuSK, and for the chemical connections between the MuSK complex and various other proteins implicated in synapse formation (*Science*, 29 March, pp. 1807 and 1867). Eventually, neurobiologists think this search will move from the muscles to the brain. "There's a lot of agrin in the brain, and it seems likely that agrin is important for the formation of brain synapses," says Sanes, who plans to look for defects in central synapses in agrin-deficient mice. If he finds some, those could provide clues to the way the brain forms. "Now that," he says, "would be cool."

**–Ingrid Wickelgren**

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