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RESEARCH NEWS

APRIL 27, 2001

Brain-Wiring Molecule Also Plays Role in Muscle Development

Researchers have discovered that a potent chemical signal known to guide the wiring of neurons in the developing nervous system also directs migrating muscle fibers to their proper connections. More surprising, however, say the scientists, is that the signal initially repels muscle cells, and later becomes a powerful attractant. The discovery of the signal's dual role and its drastic turnabout shows how tissues may use the same kinds of signals for very different purposes during development, say the scientists.

The research team, which included Howard Hughes Medical Institute (HHMI) investigator Corey S. Goodman, Sunita G. Kramer, Thomas Kidd and HHMI predoctoral fellow Julie H. Simpson at the University of California, Berkeley, published its findings in the April 27, 2001, issue of the journal *Science*.

The scientists found that in developing *Drosophila* embryos, the axon guidance protein Slit repels embryonic muscle cells, called mesodermal cells, at an early point in their growth. This repulsion occurs when Slit plugs into a receptor called Robo, which is found on the surface of mesodermal cells. When the mesodermal cells reach a point in development where they must find the appropriate attachment site on muscle cells, their Robo receptors undergo a still-mysterious transformation that leads to their becoming attracted to attachment sites that produce Slit.

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>
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"We originally discovered Slit as a repellent for axon guidance in the developing nervous system," said Goodman, who added that fellow HHMI investigator Marc Tessier-Lavigne and his colleagues had discovered another function for Slit in mammals. "But when we started to look around the organism in our case the fruit flywe noticed other times and places during development when Slit appears outside the nervous system."

That discovery was not unexpected, said Goodman, because other axon-guidance molecules have been shown to come and go at different times during development in other types of cells. "It’s as if they could be involved as attractants and repellents in other kinds of cell migrations and cell movements in other tissues," he said.

Goodman and his colleagues were keen on studying Slit's role in mesodermal tissues because they grow by extending themselves in much the same way that axons extend themselves toward their target cells. And, like growing neurons, the growing muscle cells must wend their way through intricate pathways to make precise connections.

Sunita G. Kramer, lead author of the *Science* paper, found that Slit was expressed at some muscle insertion sites and some muscle cells expressed the Robo receptors as they seek insertion sites. Importantly, she found that those Robo-expressing mesoderm cells seemed to be attracted to Slitwhich is the opposite of Slit's role in axon guidance. The scientists found that knocking out Robo in mesoderm cells made them oblivious to Slit. Conversely, adding Robo to mesoderm cells that normally lacked it made them home in on insertion sites expressing Slit.

In earlier studies, Goodman's laboratory showed that it was possible to engineer the Robo receptor to transmit a "counterfeit" internal signal that instructed cells bearing the re-engineered Robo receptor to be attracted to Slit. Thus, they theorized that their observation in fly embryos of a switch from Slit repulsion to Slit attraction was due to natural changes in the composition of the Robo receptor or the cell's internal interpretation of the Robo signal.

"We knew that these mesodermal cells start off their life after gastrulation being repelled by Slit," said Goodman. "And we've observed in the embryo that two hours later, these cells change their differentiation and begin to line up and become 'muscle pioneers' that start to fuse with one another to make the first muscle-type structures. And it is then that some of these cells are still expressing Robo, and they head right for Slit insertion sites.

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Although Goodman and his colleagues do not understand the change in Robo that transforms it from Slit-repulsive to Slit-attractive, they plan to explore the molecular basis for such transformation. Such changes in Robo might consist either of the addition of a new function-altering subunit to the Robo receptor, or a change in some metabolic state inside the cell that affects the Robo signal. Studies in Goodman's laboratory, as well as in those of colleagues Tessier-Lavigne and Mu-ming Poo at the University of California, San Diego, hint that either of such function-switching mechanisms is feasible.

"The possibility that such changes could switch repellent receptors to attractants has raised the possibility of therapeutic applications," said Goodman. "For example, in cases of spinal cord injury, where neurons are repelled from reconnecting, might it be possible to alter the neurons so they can be attracted."