SOUTHWESTERN NEWS

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RESEARCHERS AT UT SOUTHWESTERN DISCOVER HOW NEURONS COMMUNICATE TO 'WIRE' DEVELOPING BRAIN

DALLAS – Sept. 13, 2001 – Researchers at UT Southwestern Medical Center at Dallas have discovered a biochemical pathway that helps describe how neurons in the brain and spinal cord form their connections. Further study into the new data, published in today's issue of *Nature,* could lead to discoveries in nerve regrowth and regeneration.

"By learning how nerve fibers grow and form connections in the embryonic brain and spinal cord, we may ultimately be able to determine how to coax nerves to regrow and regenerate," said Dr. Mark Henkemeyer, assistant professor in the Center for Developmental Biology at UT Southwestern.

The research focuses on a specific group of receptors and ligands that are widely expressed in the developing nervous system. Normally, ligands produced by one cell bind to their corresponding receptor, which is expressed on target cells. This causes a change in the receptor, allowing it to transduce signals into the receiving cell. Although the body contains a vast array of different classes of receptors and ligands, Henkemeyer and his team have been working to learn how a particular group of such molecules, the Eph receptors and ephrin ligands, communicate biochemical signals between two cells.

Earlier discoveries by Henkemeyer and his colleagues uncovered functions for the Ephs and ephrins in mice.

"We found that these molecules communicate important signals that guide the growing tips of embryonic nerve fibers (the axon growth cone) and, therefore, help form networks of neurons and synapses in the brain in a process called axon pathfinding," Henkemeyer said. "We're trying to define the cellular and biochemical basis of how neurons can establish all these connections."

The entire circuitry of the brain and nervous system is controlled by this pathfinding, which leads to the formation of intricate and highly precise connections.

"I like to view the brain as the amazing organic supercomputer," Henkemeyer said. "But what's most amazing is that, unlike the supercomputers that humans assemble with their hands,

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neural networks, which are much more complicated than any man-made computer, self-wire during embryonic and postnatal development. That's the big mystery – trying to figure out how the nervous system self-wires.

"The key message of this present study is something that we've been working on for many years. When I first came to UT Southwestern to set up my laboratory, we realized that the Eph receptors and ephrins are important partners in axon pathfinding. Before then, everyone thought the ephrins were the ligands that bound to the Eph receptor on the axon, which then turned on the axon pathfinding signal. What I discovered, and what we continue to work on today, is that the ligands — the ephrins themselves – are also receptors."

This finding was unprecedented, Henkemeyer said. "For the most part, everyone thought ligands bind receptors and receptors send signals, and, all of a sudden, we're saying, 'No, the receptor is actually the ligand, and the ligand is the receptor.'"

Researchers then labeled the traditional concept of the receptor-mediated signal as a "forward" signal to distinguish it from the "reverse" signal that the ephrin ligands transduce into their own cell.

"We laid out the hypothesis five years ago that the ephrins were also receptors and that they transduce what we call the 'reverse' signal, and we also proposed that the 'reverse' signal was important in axon pathfinding," he said.

The present work now published in *Nature* is an extension of the earlier description of "reverse" signaling. The current study describes in detail the biochemical signal transduction cascades that ephrins can transduce into their cell.

"Although a tremendous amount of research remains to be carried out," Henkemeyer said, "we are one step closer to figuring out how the brain and spinal cord wire themselves up."

The study represents five years' worth of work by Henkemeyer and UT Southwestern Ph.D. candidate Chad Cowan, who received the 2001 Nominata Award, the top award from the Southwestern Graduate School of Biomedical Sciences, for his thesis research and studies.

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