SOUTHWESTERN NEWS

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UT SOUTHWESTERN SCIENTIST UNCOVERS NEUROLOGICAL LINKS

DALLAS — July 12, 1996 — A scientist from UT Southwestern Medical Center at Dallas has described for the first time how regulatory proteins called receptor tyrosine kinases play a vital role in controlling pathfinding activity in the mammalian brain.

In an article today in the journal *Cell*, Dr. Mark Henkemeyer, assistant professor of cell biology and neuroscience, demonstrates the role of tyrosine kinases in controlling the pathfinding of axons, thin, cellular extensions of neurons used to transmit electro-chemical impulses, in the mammalian brain.

Henkemeyer and his colleagues focused on the Eph family of tyrosine kinases, which have 13 distinct members. Tyrosine kinases are believed to control many aspects of cell growth and development by functioning in key biochemical cell-signaling pathways. Although many different tyrosine kinases have been shown in recent years to play important roles in cancer cells, little is known about their true functions in normal cells and during embryonic development. During the last two years, Henkemeyer and a number of other independent groups have reported preliminary indications that Eph receptors, including the one called Nuk, may be involved in a complex process called axon pathfinding.

A highly sophisticated network of axons form the circuitry required for cell to cell communication within the brain and other parts of the nervous system. These networks are somewhat analogous to the wiring and circuit boards of computers.

"Figuring out the biochemical signals that control how axons find their way as the brain develops has been a Holy Grail for researchers," Henkemeyer said. "We're now starting to understand."

Henkemeyer and his colleagues created laboratory mice that lacked the Nuk protein receptor and discovered that they survived to adulthood and did not appear to suffer physical abnormalities. The researchers began to focus more closely on the lack of Nuk, searching for the ways that it might affect nervous system development. After further study, they found

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that mice lacking Nuk were born without an anterior commissure, an important bundle of nerves that crosses the midline of the brain and connects the temporal lobes of the brain's cerebral cortex. In these mice, most of the axons forming the posterior tract of the anterior commissure migrated incorrectly to the floor of the brain, resulting in a partial breakdown of the communication between the left and right sides of the brain. The study's results suggest that Nuk plays a vital and unique role in the pathfinding of specific axons in the nervous system.

This type of developmental brain damage, Henkemeyer said, might not be obvious upon first inspection of the mice, which explains why the mice that lacked Nuk appeared fairly normal. But further tests may reveal effects from this reduction in neuron communication between the two temporal lobes. The brain has additional commissural axon tracts that connect the left and right hemispheres of the cerebral cortex, which may compensate for the loss of the anterior commissure.

Studies related to the human Nuk protein receptor are still years away. Scientists cannot predict how the abnormalities noticed in the test mice might affect overall brain function in humans, Henkemeyer said. These studies, however, have provided important information about the nature of the molecular signals used to guide axons as they find their targets.

Henkemeyer joined the UT Southwestern faculty this spring after several years with the Samuel Lunenfeld Research Institute of Mount Sinai Hospital in Toronto. Henkemeyer has continued the work he began with colleagues in Toronto and Germany in his new laboratory in Dallas.

Other researchers involved in the study were Drs. Jeffrey T. Henderson, Tracy M. Saxton, John Roder and Tony Pawson, all of Mount Sinai Hospital and the University of Toronto, and Drs. Donata Orioli and Rudiger Klein of the European Molecular Biology Laboratory.

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