SOUTHWESTERN NEWS

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SCIENTISTS IDENTIFY NOVEL COMPONENT OF CELL-FATE PATHWAY

DALLAS — September 23, 1999 — Researchers at UT Southwestern Medical Center at Dallas have identified a new component of a key pathway essential for the proper development of all animals -- from worms to humans. The discovery should lead to a better understanding of the molecular and biochemical details that control cell fate and growth and may permit scientists to influence developmental processes, like those that lead to cancer.

The new component, casein kinase I (CKI), adds another step to the preliminary outline of how the Wnt-signaling cascade functions. Dr. Jon Graff, assistant professor in the Center for Developmental Biology, and colleagues describe CKI's integral role in the pathway in the lead article in the Sept. 23 issue of *Nature*.

"We know that the Wnt pathway is critical for normal development and that there are many types of human cancers that have mutated Wnt components," Graff said. "If we thoroughly understand how this pathway functions, we should be able to design new genetic and pharmacological approaches to develop preventive measures or cures for those cancers."

The Wnt signaling pathway regulates development by altering gene expression through a series of interactions. Wnt signals bind with receptors on the cell surface and pass into the cell. There they prevent another protein from shutting down the Wnt pathway. This protein then joins with deoxyribonucleic acid (DNA)-regulatory co-factors

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and enters the cell's nucleus where it binds to the DNA of Wnt-target genes to influence gene expression.

Graff and colleagues identified CKI as a Wnt cascade component through experiments in frogs and worms. The component is a member of a family of enzymes that transfers phosphate groups from a donor to an acceptor protein, often leading to an increase in the latter's activity. Although CKI's function was previously known, its biological role was not. The scientists found that CKI helps to transmit Wnt signals after the signals enter the cell and before the protein that negatively controls the Wnt pathway is turned off.

Graff and co-workers graphically demonstrated CKI's role in frogs, where Wnt signaling is known to control the dorsal axis. If additional CKI is injected into frog embryos, a second dorsal axis develops and the resulting embryos have a duplicated dorsal body plan just like conjoined twins. When the researchers destroyed dorsal structures in frog embryos with ultraviolet irradiation, they could "rescue" them by injecting CKI. In the worm *Caenorhabditis elegans*, Graff and collaborators showed that blocking CKI disrupted Wnt signaling by producing the same type of abnormal worm that results from blocking previously known Wnt signals.

Other UT Southwestern scientists participating in this research were graduate student John Peters, and postdoctoral fellows Dr. Renee McKay and Dr. James McKay, all of the Center for Developmental Biology.

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