UT SOUTHWESTERN MEDICAL CENTER NEWS

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Worm hormone discovery may aid fight against parasitic disease

DALLAS – March 9, 2006 – New research at UT Southwestern Medical Center shows that on a biochemical level, hormone-like molecules in tiny worms called nematodes work similarly to the way in which certain hormones work in humans – findings that one day may help eradicate worm infections that afflict a third of the world's population.

UT Southwestern researchers have discovered a molecule that activates genes involved in the development and reproduction of *Caenorhabditis elegans*, a common research worm about the size of a pinhead.

In a study available online and appearing in the March 24 issue of the journal *Cell*, UT Southwestern scientists describe how the molecule, called a ligand, acts like a hormone, the first such hormonal ligand identified in *C. elegans*.

Like a key fitting into a lock, the newfound ligand binds to a protein in the cell's nucleus called a nuclear receptor, a receptor designated DAF-12. Once that binding occurs, DAF-12 activates other genes that allow the worm to develop through its normal stages, reach maturity and reproduce.

When the researchers blocked that hormonal signal by engineering mutant worms that couldn't manufacture the ligand, however, the mutants' development stopped before they reached maturity. Instead, the worms went into a "resting" stage called the dauer diapause, in which they don't eat or reproduce. When the researchers provided the mutants with the missing ligand, it prevented the dauer stage, and the animals continued to develop normally.

"This pathway in worms is remarkably similar to hormonal pathways in humans," said Dr. David Mangelsdorf, chairman of pharmacology at UT Southwestern and senior author of the study.

The experiments by Dr. Mangelsdorf's team are related to how hormone-replacement therapy works in humans. For example, in patients with Addison's disease, the adrenal glands do not produce enough of the steroids cortisol and aldosterone; in some cases, these glands produce none at all. Replacing the missing hormones through replacement therapy can relieve the symptoms of the disease, much as providing the missing ligand to the worms restored their normality.

"The conservation of this pathway is remarkable," said Dr. Mangelsdorf, an investigator in UT Southwestern's Howard Hughes Medical Institute (HHMI). "This line of investigation has been much sought-after in terms of how the DAF-12 protein works and whether it had a hormonal regulator. Mother

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Nature has used this system from the very simplest nematode worms up to humans, not only employing the same types of proteins to do the job, but also the same types of hormones."

The dauer diapause occurs naturally in *C. elegans* when the worm senses from its environment that conditions are not favorable for maturing, such as when food is scarce. Dr. Mangelsdorf said cholesterol and other signals derived from the worm's food source are required to launch the series of biochemical events leading to the production of the hormonal ligand and continued development. Without these environmental signals and the ligand to activate DAF-12, the worm's life remains suspended.

The UT Southwestern research also may aid in the fight against human disease because the dauer diapause stage of *C. elegans* is very similar to the infective state of parasitic nematodes. According to the World Health Organization, such parasites infect about 2 billion people worldwide and severely sicken some 300 million, at least 50 percent of whom are school-age children.

In the infective state, parasitic nematodes, such as hookworms, remain in a larval, "resting" stage until they enter the human body, where they eventually migrate to the intestine and begin to mature. Dr. Mangelsdorf is investigating whether the homologue of DAF-12 in parasitic nematodes may regulate their maturing activity as well. If so, he said, the same pathway could be exploited to eradicate the pests, either by keeping them perpetually in an immature state, or by coaxing them to mature before a food source is available.

Other UT Southwestern authors on the paper are lead author Daniel L. Motola, an M.D./Ph.D. student in the Medical Scientist Training Program; Dr. Carolyn Cummins, a research fellow in pharmacology and an HHMI research associate; Dr. Kamalesh Sharma, a postdoctoral fellow in internal medicine; Tingting Li, student research assistant in pharmacology; and Dr. Richard J. Auchus, associate professor of internal medicine. Other authors were from Baylor College of Medicine and the Van Andel Research Institute in Michigan.

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