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RESEARCH NEWS

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Worm Studies Unearth New Drug Target for Parasitic Infections

A team of Howard Hughes Medical Institute (HHMI) researchers has hit paydirt by plumbing the biochemical intricacies of a lowly soil-dwelling worm. Their discovery has revealed a new target for drug therapy that may help alleviate parasitic worm infections that afflict tens of millions of people worldwide.

The new studies, conducted by an HHMI research team led by David J. Mangelsdorf of the University of Texas Southwestern Medical Center in Dallas, were reported March 10, 2006, in an early online publication in the journal *Cell*. The study identifies two hormone catalysts that trip a genetic signaling pathway central to reproductive development, lifespan and, in worms, a state of dormancy that mimics hibernation.

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> **— David J. Mangelsdorf**

In making the discovery, we confirmed what the genetics told us, said Mangelsdorf, explaining that the gene and its role in influencing reproductive development were known.

What was not known, however, was the chemical agent or agents that, in response to signals from the environment, switch the gene on or off. Mangelsdorf and his colleagues have found that switch with their identification of two hormones that modulate that gene.

The finding is remarkable, according to Mangelsdorf, because it reveals key hormonal players in a process in invertebrates that is mirrored in humans. These results suggest that this biological process was forged deep in evolutionary history and is shared by all animals. Its practical upshot, however, is the identification of new targets for drugs that could disrupt development of parasites, such as hookworm, that affect human health, mostly in the developing world, and in agriculture.

If you inhibit this pathway, you can prevent (the animal) from going into its reproductive cycle, Mangelsdorf explained. It means there is potential for designing new drugs that target parasites.

Mangelsdorf and his colleagues used the genetic model, *Caenorhabditis elegans*, a roundworm that lives in the soil and is a workhorse of biomedical research. Like other worms, *C. elegans* responds to environmental cues. For example, when food is in short supply or when other conditions such as overcrowding do not favor reproductive success, the worm slips into a state of dormancy that prevents it from developing into a sexually mature adult.

Although scientists suspected hormones might play a role in regulating this behavior, no hormones had ever been found in *C. elegans*. Now, Mangelsdorf's group has found two, both of which modulate the activity of the gene through a nuclear receptor known as DAF-12.

Nuclear receptors are proteins that reside inside cells. They depend on chemical messengers known as ligands, which enter the cell, dock with the nuclear receptors, and initiate a chain of chemical reactions.

In the case of *C. elegans*, when the larval animal is confronted with a scarcity of food or a crowded environment, it can go into a state known as dauer diapause in response to a chemical cue. In that state, development is arrested and the worm does not eat or reproduce, and the effects of aging are delayed. When conditions get better, the same chemical signaling process can prompt the worm to resume feeding and develop to sexual maturity.

Each receptor is like a lock that has a unique specificity for a (hormone) key, Mangelsdorf said. The key can turn on a program that allows an animal to do a number of different things. One of those things is that it allows the animal to develop into a reproductive adult.

Knowing that hormones play a central role in the process and knowing the identity of those hormones may make it possible to develop new drugs that can interfere with worm's maturation.

Such knowledge may be a boon to treating parasitic infections such as hookworm. Hookworm is an intestinal parasite that affects as many as one billion people, mostly in tropical or subtropical regions of the world. It causes mild diarrhea and cramps, but severe infection can cause serious problems for newborns, children, pregnant women and the malnourished.

There is a need for new drugs to treat hookworm and other parasitic afflictions, Mangelsdorf said, and his group's findings may help speed the process. For example, medicines that target nuclear receptors can be administered orally. Ease of administration lowers the cost of drug development and makes treatment easier, especially in the developing world where health care is at a premium.

It is much easier to develop orally-ingested drugs, Mangelsdorf explained. There are many drugs, like contraceptives, that are directed to nuclear

receptors.

Results of the new study are of interest to biologists because they suggest an evolutionary commonality between nematodes and humans that wasn't completely suspected, Mangelsdorf said. The hormone signals in different tissues to mediate its effect. That is remarkably similar to what happens in animals, including humans. The pathway is conserved.

Coauthors of the *Cell* paper include Daniel L. Motola, Carolyn L. Cummins, Kamalesh K. Sharma, Tingting Li and Richard J. Auchus, all of the University of Texas Southwestern Medical Center in Dallas. Other coauthors include Veerle Rottiers and Adam Antebi of the Baylor College of Medicine; and Yong Li, Kelly Suino-Powell and H. Eric Xu of the Van Andel Research Institute in Grand Rapids, Mich.