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## Manipulating Worms' Life Cycle Could Thwart Infection

Research has revealed a novel way to tinker with the life cycle of parasitic worms—suggesting new avenues to attack or prevent infections such as hookworm that plague an estimated 1.3 billion people worldwide.

The findings, published May 25, 2009, in the Proceedings of the National Academy of Sciences, build on previous research in the harmless, free-living roundworm *Caenorhabditis elegans*. That work illuminated a signaling pathway that initiates or ends a hibernation-like state in which *C. elegans* larvae stop eating and do not reproduce. The dormant state is called dauer diapause.

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The new study, by Howard Hughes Medical Institute investigator David J. Mangelsdorf and colleagues, has identified a similar pathway shared by several parasitic roundworms: the threadworm *Strongyloides stercoralis*, a human parasite common in the tropics and subtropics, and species of hookworm, *Ancylostoma* spp. and *Necator americanus*, that infect humans and dogs. In these parasites, the pathway impacts stage 3 infective larvae—a state of development similar to dauer diapause in *C. elegans*.

In all of the worms, the pathway acts through a nuclear hormone receptor – a protein inside the cell that is activated by steroid hormones. Nuclear receptors are a common pharmacological target in modern medicine. For instance, oral contraceptives and hormonal therapies for breast and prostate cancer target nuclear receptors.

"The pathway in free-living nematodes is conserved in parasitic nematodes," said Mangelsdorf, who is at the University of Texas Southwestern Medical Center at Dallas. These pathways are also similar to a pathway in humans and other mammals that regulates metabolism and nutrient storage after eating.

The investigators also found that *S. stercoralis* responds to a steroid-hormone-like substance known as dafachronic acid that can fool larvae into perceiving that they are in a host before they actually infect the host.

“It forces them out of their infectious state,” Mangelsdorf said of the dafachronic acid. “But since they’re not in a host, they can’t go through their complete reproductive cycle, and they die.”

Unlike dafachronic acid, current treatments for infectious worms attack only adult forms of the parasites. That allows *S. stercoralis*, which can live its entire life cycle inside the host, to persist despite treatment. “People who are infected chronically may never get rid of it. Even if you attack the adult, if there are any juveniles or eggs left it can come back,” Mangelsdorf said. Drugs that mimic dafachronic acid might provide a more effective alternative, he said.

To get a better understanding of how such drugs might work, the team used x-ray crystallography to reveal structurally how two forms of dafachronic acid bind to a nuclear receptor, like a key in a lock, to influence the pathway. Each form binds differently to the receptor, known as DAF-12, Mangelsdorf said. One acts as an agonist, or activating hormone, which would prompt the larvae to begin feeding before they are in the proper environment to do so. The other form binds to the receptor, but does not activate it and may function as an antagonist, which would block the parasite’s normal processes in the host organism.

“That suggests different drugs can be developed that target not only specific species of these nematodes, but that target them in unique ways,” Mangelsdorf said. “Both are advantageous. With an antagonist you might treat the host; with an agonist you might treat before the parasite gets in the host”—for instance, in contaminated soil.

The group also found that although the DAF-12 receptors appear in many parasitic worms, they differ subtly from one species to the next. “These differences can be a powerful pharmacological tool,” he observed, explaining that variations could be exploited to develop treatment compounds individualized for each species, for instance, to allow harmful nematodes to be targeted without killing beneficial nematodes in the soil.

Researchers looking for treatments for parasitic worm infections can begin screening chemical compounds to see whether they have an impact on the crucial receptors, Mangelsdorf said.

Targeting the enzyme that produces a hormone can also be an effective treatment strategy. But while the researchers have found the nuclear receptors in all the parasitic worms they’ve checked, they haven’t been able to find anything similar to DAF-9, which makes the dafachronic acid hormone in *C. elegans*. Mangelsdorf said it’s possible that the parasite gets the needed hormone from its host, or hijacks a host enzyme similar to DAF-9 to make the hormone.

Mangelsdorf's team at UT Southwestern collaborated with researchers at Van Andel Research Institute, The George Washington University Medical Center, Argonne National Laboratory, and the University of Pennsylvania on the study.