

No More Worming Around

DISRUPTING A WORM'S LIFE CYCLE COULD BE THE KEY TO ENDING PARASITIC INFECTION.

The trick to killing roundworms—such as hookworms and threadworms, which infect humans—may be to force the parasites to grow up too quickly. HHMI investigator David J. Mangelsdorf discovered that the molecular pathway governing how the harmless roundworm *Caenorhabditis elegans* exits a hibernation state controls the transition between life stages in many parasitic worms. He's figured out a way to intervene in that pathway and kill larvae—something existing drugs can't do.

In 2006, Mangelsdorf's team at the University of Texas Southwestern Medical Center at Dallas identified molecules—dafachronic acids—that bind to DAF-12, a receptor involved in *C. elegans* longevity. They found that the receptor is a checkpoint for worms exiting dauer diapause—a dormant state that *C. elegans* larvae enter when they perceive low temperature, crowding, or a lack of food. When the worms sense more favorable times, they produce dafachronic acids, which activate DAF-12, ending dauer diapause by turning on genes involved in reproduction and food metabolism.

Mangelsdorf's group has now shown that the parasitic worm *Strongyloides stercoralis*, among others, also has DAF-12. While these parasites don't enter dauer diapause, they do go through a similar dormant stage. So-called stage 3 infective larvae (iL3) keep

their metabolism low until they sense a friendly environment inside a host. Taking hints from the *C. elegans* pathway, Mangelsdorf and his collaborators treated the iL3 parasites with dafachronic acid. It forced the worms out of their infectious state but not fully into the next life cycle stage—the worms died before they could reproduce, the team reported in a *Proceedings of the National Academy of Sciences* article that appeared online on June 2, 2009.

The current drug of choice to kill *S. stercoralis* targets adult parasites—eggs and larvae inside the host remain viable. Using dafachronic acid to force larvae out of their infectious state and kill them could end the hard-to-stop cycle, says Mangelsdorf. His lab is screening synthetic compounds for drugs that could mimic dafachronic acid's effects and is looking more closely at the biochemical pathways that DAF-12 controls. ■

—SARAH C.P. WILLIAMS



Strongyloides parasites increase their metabolism and express a whole new set of genes once they've entered a host.

IN BRIEF

Buenos Aires and the National Research Council of Argentina, zapped cells with a strong form of radiation, called UV-C, which is normally blocked by the ozone layer. He and his collaborators looked inside the cells to determine how the radiation affected gene expression.

The UV radiation affected many genes, among which were two genes involved in apoptosis—cell suicide. The messenger RNAs from the genes, *Bcl-X* and *caspase-9*, can be spliced into two forms—one that promotes cell suicide and one that blocks it. The UV-C caused the switch from the form that keeps cells alive to the form that kills cells. Even in cells missing a protein that normally triggers the switch in *Bcl-X* and in *caspase-9*, the UV-C was enough to make the change. The team further explained how the switch was made, and their results appear in the May 15, 2009, issue of *Cell*.

Kornblihtt plans to repeat the experiments with UV-A and UV-B, the lower energy forms of UV radiation, which are the reasons we slather on sunscreen.

THE BREAST-BRAIN BARRIER

It takes a special set of skills for breast cancer to spread to the brain and grow into a new tumor. The spread is slow, but

deadly—cancers that have spread, or metastasized, from one area to another account for 90 percent of cancer deaths. HHMI investigator Joan Massagué, of Memorial Sloan-Kettering Cancer Center, has published the first account of just what it takes for breast cancer to invade the brain.

Massagué implanted tumor cells from an advanced breast cancer patient into mice. His team then isolated cells that spread to the animals' brains. They found 243 genes expressed at abnormal levels and narrowed them down to 17 by looking at their activity in clinical tumor samples.

Knowing which genes allow a cancer to spread may help doctors predict how likely an individual patient's tumor is to metastasize and could lead to targeted drugs. Already, Massagué's group has discovered that patients with breast cancer expressing some of the 17 genes are more likely to experience brain metastases. The research appeared in *Nature* on June 18, 2009. The researchers hope to further characterize the roles of the genes within the cancer cells.

FROM SIDE TO SIDE

To the untrained eye, the mass of cells that make up an embryo may look like a

jumbled mess, but each cell must be in the right spot at the right time for an organism to develop correctly. Faulty cellular orientation can lead to problems such as spina bifida, polycystic kidney disease, and metastatic cancer. Two genes that help cells determine their orientation have now been identified by HHMI international research scholar Jeffrey L. Wrana. The genes—*Smad ubiquitin regulatory factors*, or *Smurfs*—help cells move and distinguish front from back as well as top from bottom.

Wrana and his colleagues at the University of Toronto genetically engineered mouse embryos that lack the two *Smurf* genes and observed what happened. The embryos failed to develop correctly—appearing short and wide when they should have been long and thin and improperly forming the tube that becomes the spinal cord. The anomalies didn't stop there: hair cells in the inner ear, normally organized neatly, were scattered in all directions.

To explain how *Smurf* genes control a cell's sense of space, or polarity, the researchers looked for other proteins that interact with *Smurf* gene-encoded proteins. They found two, the team reports