

FEBRUARY 10, 2006

Worms May Help Reveal Secrets of Peculiar Tumors

Howard Hughes Medical Institute researchers have developed a new genetic model in the nematode *Caenorhabditis elegans* that may help scientists understand how a specific kind of tumor develops from germline cells.

The tumors are called teratomas, a name derived from *teroton*, the Greek word for monster. True to their name, teratomas are a monstrous mix of cell types - usually appearing with bits of hair, teeth, and bone wrapped into a metastatic ball.

Researchers have had a difficult time understanding how and why these tumors form. But an article published in the February 10, 2006, issue of *Science*, provides new clues to some of the genetic missteps that may occur. In the article, HHMI investigator James Priess and colleagues at the Fred Hutchinson Cancer Research Center in Seattle report that they switched off two genes in *C. elegans*, prompting gonad cells to grow into teratomas.

"When I first looked, I didn't see anything. Then the whole thing convulsed. Muscle cells had developed inside the gonad – a place where there isn't supposed to be any muscle"

- James R. Priess

"My postdoc, [first author] Rafal Ciosk, called me over to the microscope and said, 'Look at this,'" Priess said. "When I first looked, I didn't see anything. Then the whole thing convulsed. Muscle cells had developed inside the gonad - a place where there isn't supposed to be any muscle."

Inside the gonad of the nematode, Priess and his colleagues saw two kinds of muscle, intestinal cells and well developed neurons. "The neurons had these nice, long axons. It was very surprising," he said. Electron microscopy and other techniques confirmed the identities of the cell types that Priess and Ciosk observed inside the gonad.

The two genes the researchers switched off, *gld-1* and *mex-3*, both help regulate the expression of messenger RNA (mRNA) in germline cells. These are the cells that eventually develop into sperm and eggs. Much like embryonic stem cells, germline cells can also give rise to most other cell types through a property called totipotency. When totipotency goes awry, however, teratomas may develop. Between 15 to 20 percent of all human ovarian cancers are teratomas, as are a smaller percentage of testicular cancers.

Both GLD-1 and MEX-3 had been studied extensively, but until now, no one had made a *C. elegans* strain that lacked both proteins. In a previous study, Ciosk and Priess found that mutants lacking GLD-1 had inappropriate expression of MEX-3. This finding raised the possibility that MEX-3 might compensate for the lack of GLD-1 in certain biological processes. “In genetics, when you see something like that, the solution is to make a double-mutant,” Priess said.

The experiments reported in *Science* show that GLD-1 and MEX-3 are crucial for maintaining totipotency in the germ cells of *C. elegans*. Analogous genes with perhaps analogous functions are known to exist in human germline cells, Priess said. Similar to human ovarian teratomas, the nematode teratomas appear to result from germ cells that have entered, but not completed, meiosis. Meiosis is a specialized type of cell division in which chromosomes recombine before differentiating as sperm or eggs.

Priess and coworkers found that the double-mutant germ cells showed defects in cellular structures called P-granules prior to differentiating as neurons or muscles. “P-granules are a defining structure of germline cells, and may be related to mRNA processing centers called P-bodies in other cell types,” said Priess. “It leads to the intriguing possibility that, in the double-mutant worms, the P-granule defects lead to problems in mRNA regulation, and ultimately, to the teratoma-like growth we saw,” said Priess. “Although there’s not a lot known about how teratomas form, we now have a relatively simple model for studying them.”