Gene research holds key to ‘switching off’ leukemia

Countless *Caenorhabditis elegans* worms squirm and wrestle against one another like animated, transparent grains of rice; just smaller – less than one millimeter each in length. Seen through the lens of a microscope, the simplicity and sameness of all *C. elegans* turn their tight-knit undulation into a hypnotic dance, like a computer screen-saver or ever-changing iTunes graphic. Simplicity and sameness also make *C. elegans* an ideal organism in which to observe the genesis and growth of cancer.

“Preventing or curing cancer in humans first requires an understanding of the genetic factors underlying the development of cancer,” said Dr. Scott Cameron, a pediatric hematologist-oncologist on the medical staff at Children’s and assistant professor of Pediatrics and Molecular Biology at UT Southwestern. “We know that timely cell suicide is the body’s most effective defense against many kinds of cancer. The question is: How does a cell decide whether to kill itself, and how do cancer cells avoid this fate?”

Programmed cell death

Every cell in every animal has a built-in suicide trigger, from eels to elephants; from dragonflies to dinosaurs; from *C. elegans* to humans. Analysis of programmed cell death in *C. elegans* revealed how this pathway works. One of the circumstances that activates the programmed cell death pathway is when a cell is injured or mutated and becomes a danger to the body of which it is a part. For mutant cells to multiply, becoming cancerous, they first have to find a way to deactivate the suicide switch. The Cameron lab studies how the genetic mutations caused by leukemia and other blood disorders deactivate similar programmed cell death pathways in *C. elegans* worms and humans.

“In *C. elegans*, the ancestry and fate of every cell is known as the zygote develops into an adult,” Dr. Cameron said. “With invariant cell lineage we are able to induce specific genetic mutations and then observe the effects at the level of individual cells, tracing how, when and why single cells live and die.”

Application to children with leukemia

The work of the Cameron lab could hold significant meaning for children like Ethan Funkhouser and other children with acute lymphoblastic leukemia.

“Recently, we have found a switch that controls cell death of one cell in the developing worm. The human equivalent of that switch is one of the most commonly mutated genes in children with ALL, a Hox gene. This is powerful genetic evidence that suggests Hox mutations in children promote leukemia by preventing death of developing leukemia cells.” Dr. Cameron said. “We now know of three pathways that regulate the cell death switch in the worm. Human gene counterparts in all three pathways are cancer genes that promote cancer by preventing programmed cell death. We now need to demonstrate that in leukemia, mutations affecting Hox genes prevent cell death. Then, we can design a treatment that specifically acts on this switch to cause death of the leukemia cells.”

Half of the staff in the Cameron lab are now performing research with cancer cell lines generated from a 9-year-old with leukemia. They turn off the Hox genes and observe if, when and how the cells die to determine cell death causality.

The importance and relevance of the Cameron lab’s research are validated by funding from the National Institutes of Health, the National Cancer Institute and the Children’s Cancer Fund. NIH support began in 2005 with a five-year R01 research grant.

“There are a zillion things to try, but harder problems have been solved,” Dr. Cameron said. “It is very clear what kinds of experiments need to be done; we just have to get them done so we can provide better cancer therapies for children.”