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Protein Maintains Stem Cell Reservoir

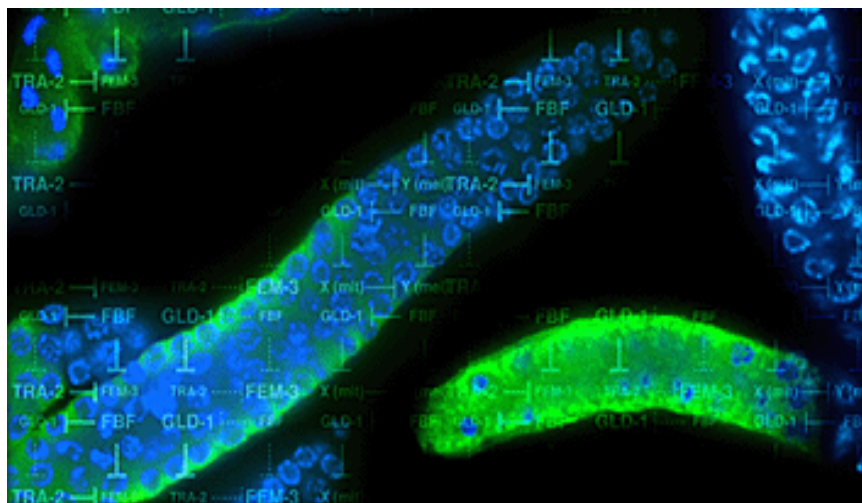


Image Title: Germline stem cell regions dissected from the nematode *Caenorhabditis elegans*, overlaid by regulatory circuitry controlling stem cells and sexual fates. - Generated by Sarah Crittenden and Adam Steinberg

Researchers studying the roundworm *C. elegans* have discovered a protein that maintains a reservoir of germline stem cells the cells that are the wellspring of sperm and eggs.

HHMI investigator [Judith E. Kimble](#) and colleagues at the University of Wisconsin-Madison reported in the June 6, 2002, issue of the journal *Nature*, that the *C. elegans* protein FBF, a member of the PUF family of proteins, is necessary for germline stem cells; without FBF, all of the germline stem cells mature into sperm.

In the *Nature* article, the scientists draw comparisons between FBF and other members of the PUF protein family, which have been identified in worms, flies and humans. The common theme among the various members of this family is that they promote cell division at the expense of differentiation, in which daughter cells become increasingly specialized.

Kimble and her colleagues discovered FBF's role in maintaining germline stem cells while studying how the protein controls the switch from making

sperm to making eggs. Since some *C. elegans* are hermaphrodites, they can switch from making sperm to making eggs. Nearly 20 years ago, Kimble discovered that a single cell in *C. elegans*, called the distal tip cell, controls germline stem cells during larval development and adulthood. Kimble has been working on the sperm/oocyte decision as a parallel project in the lab.

Since then, she and her colleagues have been dissecting the molecular controls that regulate how germline stem cells are able to simultaneously maintain exact copies of themselves while dividing to produce cells that will become sperm or eggs. In developing worms, a production line begins with stem cells at one end and proceeds to mature sperm or eggs at the other end within the worm sex organ, or gonad.

Few organisms have a single cell that governs germline fate decisions, said Kimble. *C. elegans* is a simple, manipulable system in which we can genetically pick apart the control of germline stem cells, an important and unsolved problem in biology.

The scientists discovered in 1997 that FBF (*fem-3* RNA binding factor) controls sex determination in worms. In an effort to further understand its role, they created a mutant worm in which they deleted two genes, *fbf-1* and *fbf-2*, that encode FBF. To their surprise, Kimble and her colleagues discovered that the worms carrying the gene knockouts had no germline stem cells. All of their germline stem cells had become mature sperm during larval development, and there was no reservoir for future gamete production.

Further investigation showed that FBF acts by binding to and inhibiting the messenger RNA encoding a protein called GLD-1, whose role is to drive germline cells into meiosis a specialized type of cell division involved in the creation of mature sperm and eggs. FBF represses GLD-1 in the distal germline region, thus maintaining stem cells, while germ cells move out of the distal region to become sperm or eggs. Without FBF, GLD-1 drives all the cells to become mature sperm.

The finding helps bring together a growing body of evidence showing how stem cells are regulated at the molecular level. The fact that PUF proteins are found in a variety of organisms likely means they have an important and conserved role, Kimble said.

PUF proteins control many biological events, but the primordial function or ancient function is probably to promote mitosis, said Kimble. We know FBF functions in regulating germline stem cells in *C. elegans*. While we don't yet know its role in humans, a PUF protein has been localized to human testes. My bet is that homologs of PUF proteins will be found to control germline stem cells in humans. I think that's a reasonable prediction.