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## Counting X Chromosomes to Determine Sex

In mammals, the developmental decision for an embryo to become male or remain female rests with the Y chromosome: if the Y chromosome is present, the embryo becomes male. But many species lack a Y chromosome, so the choice must be made by counting X chromosomes instead, which is not an easy task.

Barbara Meyer, a Howard Hughes Medical Institute investigator, and her colleagues at the University of California, Berkeley, have discovered a signal, which they call SEX-1, that helps the nematode worm *C. elegans* tally its X chromosomes. SEX-1, a hormone receptor found in the cell nucleus, belongs to a family of proteins widely used by animals to translate environmental cues into decisions on how to regulate gene expression. A similar molecule may be involved in the first steps of mammalian sex determination.

"The process of sex determination may differ from organism to organism, but the underlying mechanisms may be much more similar," says Meyer. She and her colleagues report their findings in the November 12, 1998, issue of the journal *Nature*. The work was partly supported by grants from the National Institutes of Health.

Among *C. elegans*, worms with two X chromosomes, or XX animals, usually develop as hermaphrodites, while those with a single X chromosome, known as XO animals, develop as males. Hermaphrodites, given a choice, will mate with males, but unlike females of other species, hermaphrodites produce sperm that they can use to fertilize their own eggs in the absence of males.

The X chromosome in *C. elegans*, says Meyer, "has at least four genes, probably five or six," that signal the chromosome's presence. All those X signals are believed to dampen the activity of a pivotal protein, called XOL-1, that processes the incoming X signals and steers organisms' sexual fates. When the X signals are abundant enough to overwhelm XOL-1, a worm will develop as a hermaphrodite. In XO animals, XOL-1 is not suppressed by many X signals and so can trigger male development.

Only one X signal had been discovered before, a gene called *fox-1*. Its product reduces the amount of XOL-1 protein that is made from messenger RNA molecules. Until now, no X signals had been found that affected the preceding step, the formation of messenger RNA molecules from the *xol-1*

gene.

The newly discovered *sex-1* gene codes for a protein that belongs to the nuclear hormone receptor (NHR) superfamily. By comparing the gene sequence of *sex-1* with that of other NHR genes, Meyer's group determined that one part of the SEX-1 protein grabs on to DNA, while another region in the protein may bind to an as yet unidentified small molecule. The small molecule might need to be present to activate SEX-1 so that it can bind DNA and turn an individual into a hermaphrodite.

Meyer points out that if SEX-1 needs to bind to a small molecule, or ligand, before being activated, such a mechanism would help ensure that no cells make a mistake in deciding sexual fate. Such a ligand would spill freely among cells and would sway even errant cells toward a hermaphroditic fate.

Whether it first needs to bind a ligand or not, SEX-1 ultimately binds to a part of the *xol-1* gene, known as its promoter, and by doing so suppresses that gene's expression. SEX-1 may prevent *xol-1* expression by simply getting in the way of factors that permit that pivotal gene to be turned on.

Still, SEX-1 is just one signal. Other X signals need to accumulate and may even cooperate to inhibit XOL-1 activity enough for normal hermaphrodite development.

None of these intricately observed mechanisms may apply beyond nematode worms. Insects, birds, and mammals have sex chromosomes that are not related to the worm sex chromosomes, or to each others. Still, in a striking parallel, a gene on the human X chromosome, *Dax1*, can also encourage female development when present in duplicate. *Dax1* also codes for a nuclear hormone receptor.

That similarity between worm and human sex determination may be a coincidence, but Meyer sees other reasons for studying worms in such detail. "NHRs are involved in cancer and many other human diseases," she points out. Worms are tractable model organisms for studying the properties and interactions of genes and proteins in detail. And certain types of genes and proteins and the interactions among them recur in seemingly unrelated processes. "It's nature being very smart and compact," says Meyer. "Nature goes along and uses whatever's there for new purposes."