New Clues to How Sex Evolves

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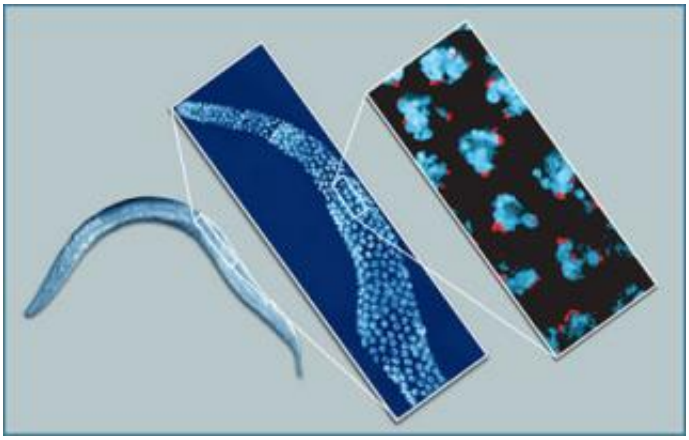
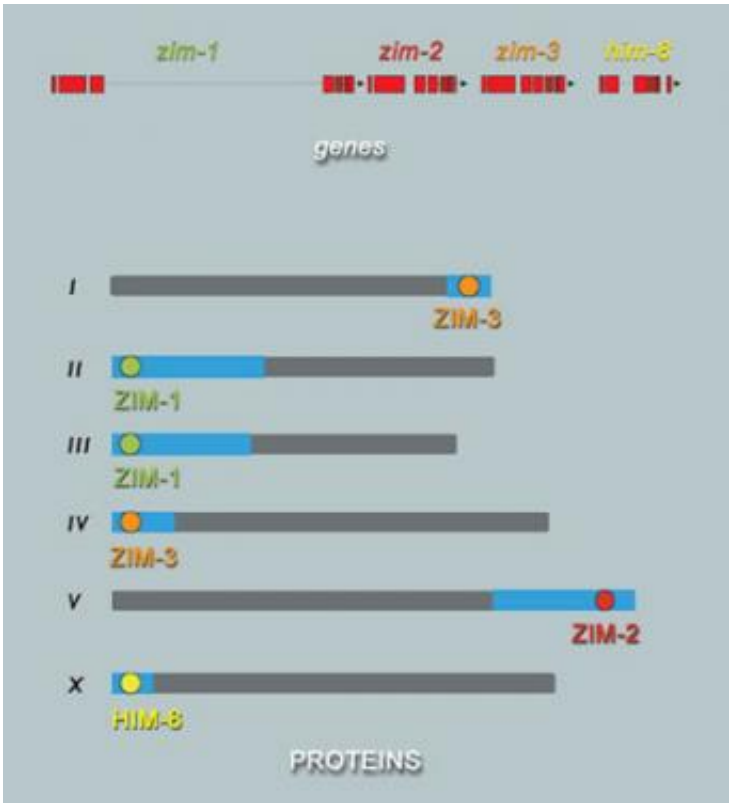


The millimeter-long, transparent nematode C. elegans (left) is ideal for observing the development of sex cells inside the worms's two large gonads (partial view, center). Antibodies label zinc-finger proteins in Pairing Centers attached to the nuclear periphery during the pairing process (red, right). Credit: Berkeley Lab

Sex is a boon to evolution; it allows genetic material from parents to recombine, giving rise to a unique new genome. But how did sex itself evolve? Researchers at the Department of Energy's Lawrence Berkeley National Laboratory and the University of California at Berkeley have found clues to one part of this complex question in ongoing studies of the nematode Caenorhabditis elegans.

Abby Dernburg, of Berkeley Lab's Life Sciences Division and UC Berkeley's Department of Molecular and Cell Biology, working with graduate student Carolyn Phillips, has identified a key family of genes

and proteins that help bring C. elegans chromosomes together during meiosis. This specialized cell division produces gametes, or sex cells, each of which has only one copy of each chromosome instead of the two copies most cells carry.



The first gene to be identified as having a role in chromosome pairing in C. elegans was him-8, which codes for the HIM-8 zinc-finger protein. HIM-8 acts on the X chromosome's Pairing Center. Three similar genes, zim-1, zim-2, and zim-3, are found adjacent to the him-8 gene and code for related proteins that act on the Pairing Centers of the nonsex chromosomes. (Pairing Centers are the blue areas of the chromosome diagrams.)

During meiosis a cell replicates and then divides twice, resulting in sperm or eggs with just one set of chromosomes each. For meiosis to

work properly, corresponding chromosomes must first identify each other, then line up accurately and stay together during the recombination process. Different organisms use different methods for these critical steps; in C. elegans, the job is initiated by regions called Pairing Centers, which are found near one end of each of the worm's six chromosome. Dernburg's lab has been studying the role of these special regions.

Last year Dernburg, Phillips, and their colleagues identified the function of a C. elegans protein called HIM-8. This protein binds to and helps bring together copies of the worm's sex chromosome (the X chromosome) to achieve stable pairing, called synapsis. Now Dernburg and Phillips have found three new genes, which they have named zim-1, zim-2, and zim-3, that perform the same functions for the worm's five additional chromosomes. Their results are published in the December issue of Developmental Cell.

All four of these genes code for different but highly related "zinc-finger" proteins, proteins that usually recognize specific sequences of DNA. Each protein acts to pair and link together one or two specific chromosomes among C. elegans's full set of six. The him and zim genes appear in tandem on a single chromosome, which raises the question of how they evolved.

"There are many families of zinc-finger proteins involved in DNA transcription, all very rapidly evolving," says Dernburg. "Gene duplication is common throughout the genome in all species, but unless a duplicated gene quickly acquires a new function, it is not likely to be conserved. The group of related zinc-finger protein genes in C. elegans offers an opportunity to address the question of how and why new zinc-finger proteins acquire new functions."

A model of reproduction

C. elegans is a tiny worm, typically a millimeter in length, admirably suited to the study of meiosis because it is completely transparent and reproduces very efficiently, producing over 200 progeny within a few days. Most C. elegans are hermaphrodites, which have two X chromosomes (XX), while some individuals are males with a single X chromosome (X0). The reproductive organs contain about half of the cells in an adult worm, and the process of meiosis can be observed at every stage, as chromosomes first come together during the pairing process and later separate during meiotic division.

One result of failed pairing of X chromosomes is a high incidence of males, with only one X chromosome. The observation that a mutant him-8 gene gives rise to a high incidence of males is what gave the gene its name.

"In all organisms, sex chromosomes do special things," says Dernburg. "For example, in species where an X and Y chromosome make a male, only very small regions of these chromosomes require control for successful pairing. So even though we saw there were nearby genes similar to him-8" — which acts only on the C. elegans X chromosome — "at first we weren't sure they performed similar functions for the other chromosomes."

Dernburg and Phillips applied "reverse genetics" to the neighboring genes, obtaining worms from the Japanese National Bioresource in which each of the three new genes had been specifically deleted. By observing meiosis (and its failures) in these knock-out worms, it was clear that one of the new genes was responsible for successful pairing of the nonsex chromosomes II and III, one was responsible for pairing of chromosome V, and the third for chromosomes I and IV.

The researchers were able to visually detect the zinc-finger proteins during meiosis and show that each protein binds specifically to the

chromosomes they help to pair. Further tracking showed that during meiosis HIM-8 and the ZIM proteins on each chromosome latch onto the cell's nuclear envelope. This activity is reminiscent of the way chromosomes attach to the nuclear envelope during meiosis in other organisms.

"In most eukaryotic species — plants, mammals, fungi, and so on — the telomeres on the ends of the chromosomes anchor to the nuclear membrane in a transient structure called a 'meiotic bouquet,'" Dernburg says. "In C. elegans it's the Pairing Centers, not telomeres, that attach to the nuclear envelope. They do so seemingly randomly, not in a single bunch; nevertheless, the association with the nuclear envelope seems to serve a similar function, which is to stabilize chromosome interactions during pairing."

Exactly how, Dernburg says, is still unknown. "Zinc-finger proteins evolve rapidly because they are modular, so that combinations of elements allow them to move quickly to new binding sites on DNA, making the Pairing Centers of different chromosomes unique," she says. "Telomeres, on the other hand, are all very much alike, no matter which chromosome they're on. It could be that C. elegans, which is hermaphroditic and grows to maturity in only three days, is under a lot of competitive pressure to reproduce quickly, and that different binding sites on different Pairing Centers makes for faster chromosome pairing and thus faster reproduction — unlike organisms that need to find a mate before they can reproduce, and mature more slowly."

Evolution under the microscope

The tandem arrangement and structural similarities of the him and zim genes suggest they all arose from a common ancestor through gene duplication and subsequent selection. This inspired Dernburg and Phillips to look at similar genes in the related species C. remanei and C.

briggsae. Like C. elegans, C. remanei has a total of four such genes, while C. briggsae has five. All code for zinc-finger proteins, all of which are distinct from one another.

"These different species of Caenorhabditis are evolving rapidly away from one another," says Dernburg. "The zinc-finger proteins bind to different sites in the Pairing Centers on their chromosomes, which prevents pairing during meiosis, so even those who mate can't produce fertile offspring."

The question remains whether new binding sites or new forms of zinc-finger protein lead rapid evolution in the worms. And there are other questions: in C. elegans, and also C. remanei, there are only four kinds of ZIM proteins that serve to initiate the pairing of six different chromosomes (in C. briggsae, only five proteins for six chromosomes), "so there must be more at work in helping the chromosomes that share the same ZIM figure out what's their proper partner," says Dernburg.

When it comes to the evolution of sex in C. elegans and its relatives, "we haven't yet figured out what makes each chromosome unique," Dernburg says. But the evidence is strong that the answer, as far as the worm is concerned, lies on the chromosomes' Pairing Centers.

"A family of zinc-finger proteins is required for chromosome-specific pairing and synapsis during meiosis in C. elegans," by Carolyn M. Phillips and Abby F. Dernburg, appears in the December, 2006 issue of *Developmental Cell*.

Source: Lawrence Berkeley National Laboratory

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