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## Researchers Gain Better Understanding of Mechanisms Compensating for Gene Dosage Differences Between Sexes

Researchers have achieved new insights into how the global control of all genes on a single chromosome can be established and maintained throughout the lifetime of an organism.

Their findings about what researchers call “dosage compensation” help explain, for example, how the cell manages to adjust the levels of gene activity on the X sex chromosomes so that females (XX) end up with the same levels of gene expression as males (XY).

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— **Barbara J. Meyer**

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The researchers, led by Howard Hughes Medical Institute investigator Barbara J. Meyer , published their findings in the February 20, 2004, issue of the journal *Science* . Meyer and her colleagues are at the University of California, Berkeley.

The basic problem facing Meyer's group and others was in coming up with an experimental way to distinguish the overall strategy by which a complex of regulatory proteins, called the “dosage compensation complex” (DCC), attaches itself to X chromosomes and spreads its influence across broad reaches of that chromosome.

Although the researchers study the roundworm *C. elegans* , many of the principles they uncover in their work are universal - true for most, if not all, organisms, said Meyer. “There are differences among organisms in how

dosage compensation works, but the essential features are similar in all organisms—in that proteins or RNA molecules bind to initial sites on the X chromosome and then spread across the entire chromosome,” said Meyer. “Because of this universality, understanding the actual mechanism of spreading is extremely important to learning how gene regulation occurs in all organisms.”

In their studies, the researchers sought to distinguish which of four potential strategies the worm's cells employ for dosage compensation. One possible mechanism might be similar to that which mammalian cells use to inactivate one of two X chromosomes during development. In mammalian cells, a single inactivation center spreads its dampening influence across the entire X chromosome. Another possibility is that it might be akin to what happens in the fruit fly *Drosophila*, in which a number of sites on a chromosome work together to recruit the DCC, and short-range spreading occurs.

A third model suggests the existence of a limited number of autonomous DCC recognition sites; once the DCC occupies a site, it does not spread, but exerts its influence on genes over a long range. This may occur by altering the structure of the chromosome. And the fourth possibility considered by Meyer and her colleagues is that myriad recognition sites exist and the DCC is regulated on a gene-by-gene basis.

To evaluate these possibilities, Meyer and her colleagues first determined which segments of the *C. elegans* X chromosome could recruit the DCC. They did this by snipping out bits of a chromosome from its entire length and testing each bit to see if it could recognize the DCC. Their analysis immediately eliminated the single-site mechanism, because the researchers identified many DCC recognition sites along the chromosome.

Additional analysis of the number, location and function of the DCC recognition sites pinpointed the second mechanism as the driver of dosage compensation in *C. elegans*. Discrete X-recognition sites attract the DCC and nucleate spreading of the complex to regions of X that lack autonomous recruitment sites.

HHMI researchers Artyom Alekseyenko and Mitzi Kuroda, who wrote a commentary on Meyer's team's studies, which was published in the same issue of *Science*, called the finding “an important conceptual breakthrough regarding such chromatin reorganization.” Alekseyenko and Kuroda, who are both at Harvard Medical School, wrote, “Although much remains to be learned, this discovery—together with current knowledge about mammalian and fly dosage compensation—provides an interesting picture of how global control of large chromatin domains or whole chromosomes may have evolved.”

As for the future of this line of research, Meyer points to several challenges. “We need to understand the exact mechanism of spreading, which I think is really important, because although the mechanisms among organisms may be different in detail, they represent a universal phenomenon.

“We also need to find as many of the autonomous chromosomal recruitment sites as possible, because we'd like to see what features of the DNA are recognized by the complex. It's possible that the dosage compensation components we've identified do not bind directly to the DNA, but that they only bind to DNA in the context of other cellular proteins that we have yet to find. And these other cellular proteins could be involved, for example, in replication or some other essential process.”

Meyer emphasized that her studies are basic in nature, but she says, “Gene expression and especially controlling large chromosomal territories is so central to biology that it's hard to imagine how better knowledge of the mechanisms underlying these processes won't have important clinical implications.”