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Spreading is key to X inactivation

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Evidence that the process of spreading of gene regulatory complexes along the chromosome is a common and crucial theme in X chromosome inactivation is accumulating with a report in the February 20 Science of investigations in the worm, *Caenorhabditis elegans*. The results showed that multiple binding sites initiate spreading of X chromosome gene regulation along the nematode X chromosome (*Science* 2004, **303:**1182-1185).

"Flies, worms, and mammals have evolved dosage compensation strategies to equalize the levels of X-linked gene expression between males and females," Barbara Meyer, Howard Hughes investigator and professor of genetics and development and a coauthor of the paper, told us.

She explained that all cases show similarities - a dosage compensation complex that is specifically directed to the X chromosome of only one sex to modulate transcript levels.

"In worms, this is related to an ancient complex of proteins called the 13S condensin complex that is involved in chromosome resolution and compaction during both mitosis and meiosis, and so it's pretty clear that the worm evolved the process of dosage compensation by stealing components that previously did for other roles and recruiting them to the new role of gene expression," she explained.

Certain proteins thus have dual roles, whose function is determined by what complex they bind to - the mitotic/meiotic complex for chromosome resolution and segregation or the dosage compensation complex (DCC) for gene regulation.

"Given there are dual functional proteins, they must be properly put on the X chromosome only in hermaphrodites," Meyer said.

Using fluorescence *in situ* hybridization and an antibody against a component of the DCC, Györgyi Csankovszki and colleagues at the Department of Molecular and Cell Biology, University of California at Berkeley, were able to find three classes of X chromosomal DNA. "We identified bits of DNA that robustly recruited the complex, bits that recruited the complex but less robustly, and then curiously we were able to find bits of the X chromosome that seemed to have no kind of recruitment ability. That was interesting because we knew that those regions of the X contained known dosage-compensated genes," Meyer said.

When the authors examined those sequences intact in the X chromosome, they observed that they could support the recruitment of DCCs. "The only interpretation that seems feasible is that there are sites of recruitment along the X chromosome. From those sites of recruitment, the complex can spread into regions of the DNA that lack autonomously recruiting sites. So there must be a mechanism of spreading that occurs in the worm."

Barbara Panning, assistant professor in biochemistry and biophysics at University of California at San Francisco, told us, "The results from this paper suggest that worms are using a mechanism that seems quite different from what's going on in other organisms in which dosage compensation is normally studied. And that's really exciting." She added, "Chromosome-wide changes in chromatin structure are

pretty much a mystery, and anything that lets us understand how they occur or how they are modulated - that's very important."

"The paper describes an elegant method by which the DNA sequences of experimentally transferred pieces of the worm X chromosome can be visualized together with the proteins of the dosage compensation complex," said Anton Wutz, from the Research Institute of Molecular Pathology in Vienna, in an E-mail to us. "The resolution of this microscopic readout [on the DNA sequence scale] is tremendously improved compared to previous studies, allowing the authors to identify regions - in the end actually small sequence elements - that attract the dosage compensation machinery."

"In the fly and mammals, spreading is part of the dosage compensation mechanism and in both species is dependent on long, noncoding RNAs. Maybe it would be a good time to start looking for an RNA in the worm dosage compensation system," Wutz said.

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