Barbara Meyer

AS in many other organisms, sex is determined in *Caenorhabditis elegans* by the difference in the number of X chromosomes: two in hermaphrodites or females (XX) and one in males (XO). Again, as in other organisms, there is dosage compensation that achieves the same amounts of X chromosome transcription in the two sexes. For her research on uncovering the molecular mechanisms underlying sex determination and dosage compensation in *C. elegans*, Barbara Meyer has been awarded the 2010 GSA Medal.

Her research began with the analysis of mutants in eight genes: *sdc-1*, *sdc-2*, *sdc-3*, *dpv-21*, *dpv-26*, *dpv-27*, *dpv-28*, and *dpv-30*, all of which were found to affect the dosage compensation process, with effects on the viability of females but with no effect in males. Mutations on the *sdc* genes disrupt sex determination as well as dosage compensation and cause the rare surviving viable XX embryos to survive as males. They act earlier in the pathway, while the *dpv* mutants affect only the later dosage compensation pathway.

Sequence analysis showed that the proteins specified by these genes were similar to the components of 13S condensin, a complex essential for chromosomal compaction of mitotic and meiotic chromosomes in organisms from yeast to man. The basic complex contains five basic subunits, two structural maintenance of chromosome (SMC) proteins, SM2 and SM4, and three associated proteins belonging to the chromosome-associated polypeptides (CAP) family. DPY-26 resembled CAP-H, DPY-28 resembled CAP-D2, and DPY-27 was similar to SMC4. These three dosage compensation gene products formed part of a complex that was shown to assemble on the X chromosomes of females. The similarity of the dosage compensation complex to condensin suggested that common molecular mechanisms were used in both processes of condensing chromosomes and X chromosome repression and made it likely that the specialized dosage compensation evolved as a modification of

the more basic and older process of chromosome compaction.

She then went on to elucidate in greater detail the structure and function of the dosage compensation complex. MIX-1, the homolog of the protein SMC-2, is also required for mitotic and meiotic chromosome segregation, and mutations in MIX-1 are lethal in both XX and XO animals. When associated with DPY-27, MIX-1 binds to the X chromosomes of hermaphrodites. Recruitment of these two factors to X chromosomes requires SDC-2, SDC-3, and DPY-30. These three factors then recruit all the other components of the dosage compensation complex, and experiments indicate that of these, SDC-2 was likely to be the component that conferred X chromosome specificity as it was the only one that could bind to the X chromosome alone. In addition, SDC-2 expression is hermaphrodite specific; there is no maternal contribution in the developing egg and *de novo* synthesis begins at around the 40-cell stage. It is repressed in males by the product of the male-specific gene *xol-1*, the master sex determination gene. This gene is regulated by the primary sex determination signal, the X:A signal, the ratio of the number of X chromosomes to the number of haploid sets of autosomes. The twofold difference in X chromosome dose is translated into an on/off state for *xol-1*. Involved in the process are a number of X-linked genes that repress *xol-1* in a dose-dependent way and include SEX-1, a nuclear receptor, CEH-39, a homeodomain protein, and an RNA-binding protein FOX-1. Both repression of transcription and obstruction of splicing are used to block expression of *xol-1* in females. In addition, there are genes whose products measure the autosomal component and that act by activating *xol-1*.

As stated above, SDC-2 is not only important for X chromosome dosage compensation but also responsible for initiating the hermaphrodite development program. It acts by binding to the regulatory regions of

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the gene *her-1* and repressing transcription. The dosage compensation complex is recruited specifically to the regulatory regions of the *her-1* gene by SDC-2; but important differences were found between the specific binding to the *her-1* gene and the more widespread binding to the X chromosome. Most specifically, it was shown that *her-1* binding was specified by SDC-3 rather than by SDC-2, which specified the more extensive binding to elements on the X chromosome, although assembly of both complexes was dependent on SDC-2.

The X chromosome sites that bind the dosage compensation complexes were analyzed by using the large (32n) nuclei of intestinal cells carrying duplications of the X chromosome. It was shown that the X chromosomes have discrete recognition elements that recruit the complex and that then initiate a spreading of the complex to generate greater coverage. A further analysis showed that there were two kinds of binding sites, *rex* sites that use clustered 12bp motifs that are highly enriched on the X chromosome and *dox* sites that cannot initiate autonomous binding and are probably the sites to which complexes disperse. It is significant that 80% of the *dox* sites are in promoters but only some of the genes undergoing dosage compensation have *dox* sites, suggesting that repression is achieved by chromosome restructuring.

In summary, this body of research has solved many fundamental problems of the regulation and the mechanisms underlying dosage compensation and sex determination in *C. elegans*. Thus the primary signal, the

X:A ratio, is read by converting a set of dose-dependent activating factors specified by autosomal genes, and repressing factors by X chromosome genes, into a binary switch on the gene *xol-1*, resulting in turning it on in males and off in the hermaphrodite. XOL-1, in turn, represses the gene SDC-2, making its expression hermaphrodite specific. SDC-2 is required for assembly of the dosage compensation complex on the X chromosome and for turning off the gene *her-1*, which is required for initiating the male program of development. Remarkably, this is carried out by the assembly of a modified condensing complex on the *her* gene, using SDC-3, which recognizes unique sequences in the promoter and second intron of the *her* gene.

The dosage compensation complex is closely related to the highly conserved 13S condensin complex and shares a number of common components with the particular example found in *C. elegans*. This has led the research in new directions toward the regulation of crossover frequency in meiosis in *C. elegans*.

Barbara Meyer's research is a paradigmatic combination of genetics coupled with powerful methods of phenotype analysis. By looking for and finding the right mutants and then studying them with the tools that are available today for *C. elegans* and for other model organisms, she has revealed the detailed mechanisms of how sex is determined in *C. elegans* and how females escape the consequences of two X chromosomes by dosage compensation.

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