Introduction to sex determination*

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C. elegans has two sexes, hermaphrodite and male. The hermaphrodite is a modified female that in the fourth larval stage makes and stores sperm to be used later to fertilize oocytes produced within the gonad of the same animal after spermatogenesis is finished. The embryos produced by self-fertilization are encased in an egg shell and initiate development within the uterus of the hermaphrodite. When they reach about the 30-cell stage, the egg-embryos are laid by the hermaphrodite through a vulva. A useful consequence of this mode of reproduction is that a single hermaphrodite heterozygous for a recessive gene automatically generates one-quarter recessive homozyotes in its brood of self progeny—a feature, shared with Mendel's peas, that helped attract Sydney Brenner to the worm in the first place. At the same time, Brenner saw that males, which can mate with and transfer their sperm to hermaphrodites to produce cross progeny, are useful to the experimentalist for making new combinations of genes. Presumably this is also why *C. elegans* has retained the male sex, which in the short term at least is completely dispensable for reproduction.

Hermaphrodites are normally diploid, with five pairs of autosomes and two X chromosomes. Males have the same five pairs of autosomes but only a single X chromosome. Nearly all gametes—sperm and eggs—produced by hermaphrodites are haplo-X and thus give rise to XX hermaphrodite self progeny, but rare males are generated through spontaneous X chromosome loss. Males produce equal numbers of haplo-X and nullo-X sperm, so that half of the cross progeny they sire will also be male.

Males and hermaphrodites are distinctly different creatures. The first three chapters in this section describe, at the level of individual cells, the major differences between the sexes and how they arise developmentally. The embryonic cell lineages in the two sexes are essentially identical, although a few cells in each sex are programmed to die sex-specifically during late embryogenesis; for example, males get rid of two cells that in hermaphrodites would become neurons required for egg-laying. But most differences between the sexes arise during postembryonic development through different patterns of cell lineage. Surprisingly, the different patterns of lineage and differentiation are driven largely by the same genes in the two sexes, although by different cell-specific patterns of gene expression. The same multiple transcription factors and core set of intercellular signal transduction systems are used repeatedly in the sex-specific developmental pathways of both sexes.

In the first chapter of this section, Scott Emmons describes those aspects of development that are specific to the male. Much of the interesting male somatic development occurs in the tail, which in the adult contains male-specific neurons, muscles, and epidermal cells that enable the male to copulate efficiently with hermaphrodites. For the development of these tissues, some blast cells common to the two sexes initiate male-specific cell lineages. In other cases, the same cells in the two sexes differentiate differently. The major male mating structures form in dramatic morphogenetic events just before the last larval molt. Although the male somatic gonad differs substantially in overall morphology from that of the hermaphrodite, the cell lineages that give rise to the two somatic gonads are clear variants of each other.

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In his chapter, Michael Herman focuses on cell fate specifications that occur only in hermaphrodites. Both sexes make use of *Hox* genes and asymmetric distributions of the Wnt pathway transcription factor POP-1/Tcf for patterning their anterior-posterior body axes, but these regulators are interpreted differently in the two sexes. The M cell, for example, gives rise in hermaphrodites to (among other cell types) muscles needed in the mid-body region for egg laying, whereas the M cell in males gives rise to muscles in the tail needed for copulation.

Paul Sternberg has written about a single hermaphrodite-specific organ, the vulva, which forms during larval development and provides an opening between the uterus and the external environment. A remarkably detailed description of the molecular events and individual cells involved in this process has emerged. Although the cell lineage that gives rise to the vulva is invariant, it depends critically on three standard intercellular signaling pathways: EGF-Ras-MAP kinase, LIN-12/Notch, and Wnt.

The descriptions of the differences between males and hermaphrodites naturally lead to the question of what makes them different. David Zarkower explains in his chapter that the difference between male fate and hermaphrodite fate for somatic cells is determined cell autonomously by a single master regulator, the transcription factor TRA-1: hermaphrodite fate is specified when TRA-1 is active, and male fate is specified when TRA-1 is inactive. This leads to two further questions, which Zarkower addresses: what makes TRA-1 active in hermaphrodites and inactive in males, and what are the targets of TRA-1 action? The answer to the first question involves a cell-nonautonomous, global sex determination pathway, which is fairly well understood and triggered by an assessment of the ratio of the number of X chromosomes relative to the number of autosomes, the X:A ratio. The second question presents a large gap in our understanding, since very few TRA-1 targets have so far been identified.

In their chapter, Ronald Ellis and Tim Schedl point out that sex determination in the germ line is not a simple recapitulation of the regulation by TRA-1 that takes place in the soma. Although the same members of the global sex determination pathway that act in the soma are required for sex determination in the germ line, the pathway operates slightly differently, and TRA-1 is not the sole final arbiter of sexual fate. In addition, as one might expect, certain germline-specific genes are needed to control germ cell fate.

Sex determination evolves rapidly, and Eric Haag's chapter is based on the idea that our detailed understanding of sex determination in *C. elegans* makes it an attractive subject for studies in comparative biology. Only two *C. elegans* genes are known to be related to genes with sex-specific roles in a wide range of animals: *mab-3* and *mab-23* affect some male cell fates and belong to the DM domain transcription factor family, along with the *Drosophila* gene *doublesex* and some vertebrate genes that also act sex-specifically. Because *C. elegans* sex determination has otherwise evolved very rapidly, the most useful inter-species comparisons are with other nematodes, as Haag indicates. Such studies should expand as the sequences of more nematode genomes become available.

No story of sex would be complete without a discussion of dosage compensation, and in the final chapter in this section, Barbara Meyer describes how hermaphrodites assemble a protein dosage compensation complex (DCC)—which is related to a chromosome condensin complex—all along their X chromosomes to dampen X gene transcription just enough to make it equal to that found in X0 males. A functional DCC is not made in males owing to the repressive effect of the gene *xol-1*, which is active in males and not in hermaphrodites. How *xol-1* is activated only in males is an interesting story told by Meyer involving X-linked repressors and autosomal activators that enable *xol-1* to respond appropriately to the X:A ratio. The status of *xol-1* expression determines both the sex of the animal—by affecting *tra-1* expression via the global sex determination pathway—and whether or not a DCC will be formed.