Genetic Control of Sex Determination in the Germ Line of *C. elegans*

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1 Introduction

How is a germ cell instructed to differentiate as a sperm or an oocyte? This is essentially a question of sex determination asked at the cellular level. Sex determination in the germ line has been elusive to experimentation in both *Drosophila* and in mice. However, in the nematode, *Caenorhabditis elegans,* control over the choice between spermatogenesis and oogenesis has proven to be particularly accessible to genetic analysis. In this chapter, we review our current knowledge of the mechanisms in *C. elegans* that influence this decision.

2 Background

2.1 The Organism, *C. elegans*

C. elegans, a nonparasitic soil nematode, is uniquely suited to genetic analyses of animal development. Its main advantages for such studies are its short life cycle (3 days), ease of maintenance, and simple anatomy (Brenner 1974). The transparency of this tiny worm throughout its development permits the direct examination of individual cells as they divide, migrate, and differentiate in the living animal. The invariant cell lineage of the somatic tissues of *C. elegans* has led to the complete description of the ancestry of all somatic structures (Sulston et al. 1983). Furthermore, the small size of the *C. elegans* genome (about 20 X *E. coli*, about 1/35th man) facilitates both classic mutational analyses and more modern molecular studies of individual genes (Sulston and Brenner 1974).

C. elegans can develop as either of two sexes (Fig. 1). Diploid animals with two X chromosomes (XX) are self-fertilizing hermaphrodites; with only a single X chromosome (XO), they are males. Reproduction in *C. elegans* can occur either by self-fertilization, in which oocytes are fertilized by the hermaphrodite's own sperm, or by cross-fertilization. The two sexes differ substantially in morphology, biochemistry, and behavior. The hermaphrodite is essentially a female that makes a limited number of sperm. Hermaphrodites possess a gonad with two equivalent

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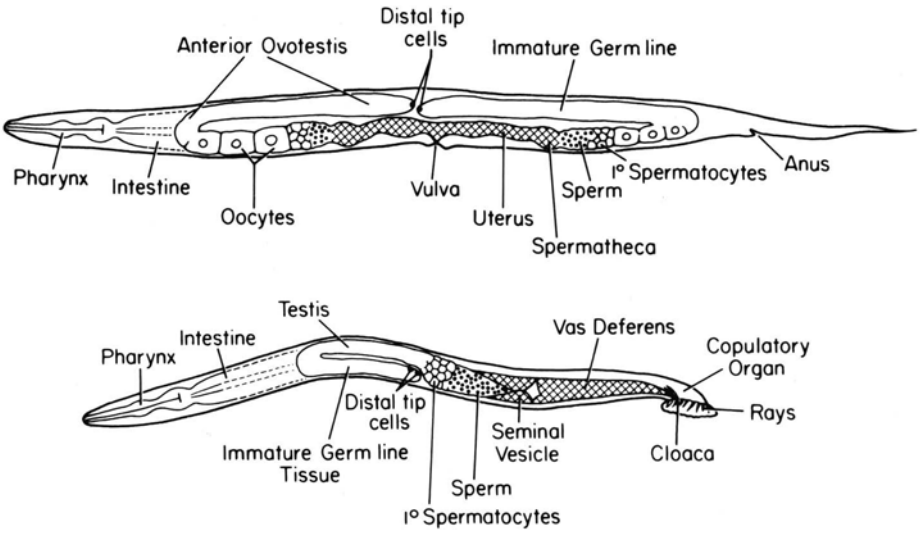

Fig. 1. Schematic diagrams of a young adult hermaphrodite (*above*) and a male (*below*). Notice the sexually dimorphic gonads (two ovotestes in the hermaphrodite, one testis in the male) and tails (a whiplike tail in the hermaphrodite, a tail specialized for copulation in the male). The somatic gonad of each is indicated by *cross-hatching,* the rest of the tubular gonad is germ line

ovotestes that meet centrally at a vulva (Hirsh et al. 1976). Each ovotestis produces first about 150 sperm, and then oocytes. Males have a gonad with a single testis that opens to the exterior posteriorly in the tail (Klass et al. 1976). The testis produces sperm continuously. During mating, the male clasps the hermaphrodite with its specialized tail and ejaculates sperm into the hermaphrodite uterus through the vulva. The male tail is an elaborate sex-specific structure composed of special nerves, muscles, and hypodermal cells that are required for mating (Sulston et al. 1980). The intestine is biochemically, but not morphologically, different in the two sexes. Only the hermaphrodite intestine produces yolk proteins (Kimble and Sharrock 1983).

Over 600 of the estimated 3000 genes in *C. elegans* have been identified by mutation. These include many genes that control various aspects of development and behavior. In the standardized genetic nomenclature of *C. elegans,* a gene is specified by a three letter code indicating its mutant phenotype and a number, e.g., *fem-1.* Mutant alleles are named by a letter specifying the laboratory of its origin and a number, e.g., *e1*, the first allele isolated by S. Brenner in England, and mutant phenotypes are given a three letter code, e.g., fem for feminized.

Three sophisticated genetic tools have recently become available for analysis of development in *C. elegans.* First, suppressor mutations have been identified that encode amber suppressor tRNAs and promote readthrough of amber (UAG) terminator codons of many genes (Wills et al. 1983). These suppressors can be used for identification of amber alleles at many genetic loci. The existence of an amber allele at a particular locus provides important evidence that the gene encodes a protein. Furthermore, the mutant phenotype of an animal homozygous

for an amber allele is often the null phenotype. Second, the generation of animals mosaic for a given activity has been achieved by the discovery that the loss of a free duplication during mitosis can be used to generate such animals (Herman 1984). Such genetic mosaic animals provide information on the cellular or tissue specificity of a gene's function. Third, a transposable element, Tc*1*, has recently been discovered in *C. elegans* (Moerman and Waterston 1984; Eide and Anderson 1985). Mutations caused by insertion of Tc*1* have already been used successfully for cloning genes by transposon tagging (Greenwald 1985).

2.2 Development and Anatomy of the Germ Line

The germ line of *C. elegans* develops as a clone from a single embryonic precursor cell, P_4 (Sulston et al. 1983). P_4 divides once during embryogenesis; its two daughter cells are the germ line progenitor cells that are present at hatching. These two cells are called Z2 and Z3. During postembryonic development, Z2 and Z3 divide mitotically to generate about 2000 nuclei in hermaphrodites and about 1000 nuclei in males. The postembryonic pattern of cell divisions in the germ line is not fixed (Kimble and Hirsh 1979). Thus, no strict cell lineage has been deduced for germ line descendants. This contrasts markedly with the development of somatic tissues that occurs by a rigidly invariant pattern of cell divisions.

The germ line nuclei are located at the periphery of a large syncytial tube, each partially enclosed by a membrane (Hirsh et al. 1976). Some germ line nuclei remain mitotic throughout the life of the animal; these mitotically dividing nuclei are loated at the distal end of the germ line tube and serve the function of stem cells for the germ line. The other germ line nuclei, located more proximally, enter the meiotic cell cycle and mature through the stages of meiosis and gametogenesis as they progress proximally (Klass et al. 1976). This means that the germ line tissue possesses a polarity of maturation with the least mature nuclei at one end (distal end), nuclei in meiotic prophase in the middle, and maturing gametes at the other end (proximal end).

Two somatic cells, the distal tip cells, regulate entry into meiosis from mitosis (Kimble and White 1981). In hermaphrodites, one distal tip cell occupies the distal end of each of the two equivalent ovotestes; in males, both distal tip cells occupy the distal end of the single testis (Fig. 1). The distal tip cells are descendants of the progenitor cells of the somatic gonad, Z1 and Z4 (Kimble and Hirsh 1979). The regulatory role of the distal tip cell was discovered by a series of laser ablation experiments (Kimble and White 1981). When both distal tip cells are destroyed by a laser microbeam, all germ line nuclei enter meiosis after only a few (one to four) mitotic divisions.

The proximal arm of the ovotestis (hermaphrodite) or the testis (male) is the site of gametogenesis. In hermaphrodites, the proximal arm is encapsulated by a somatic contractile epithelial sheath, or oviduct. In males, this arm is only partly ensheathed somatically by the most distal cells of the seminal vesicle. A detailed description of the processes of spermatogenesis and oogenesis is beyond the scope of this chapter. (For a recent review, see Kimble and Ward 1987.) Briefly, each tetraploid primary spermatocyte generates four haploid spermatids. During the

meiotic divisions, a large body of the primary spermatocyte's cytoplasm is excluded from the emerging spermatids. The spermatid matures to a spermatozoon by rearrangement of its cellular constituents to form a pseudopod. The mature spermatozoa of *C. elegans* are asymmetrical, amoeboid cells.

Oogenesis begins in hermaphrodites after about 150 sperm have been made in each ovotestis. Once oogenesis has begun, the proximal arm of the ovotestis consists of a single file of enlarging oocytes. Each of these oocytes contains a single nucleus with chromosomes in late meiotic prophase. Prior to fertilization, oocytes are halted at diakinesis of meiotoic prophase I. Both meiotic divisions occur after fertilization. When an oocyte is fertilized, the zygote moves through the spermatheca and into the uterus where meiosis of the oocyte nucleus is completed. Two polar bodies are extruded, the two pronuclei become apposed after a complex series of movements, and embryonic divisions begin.

2.3 The Global Sex Determination Genes

The initial signal for sex determination in *C. elegans* is the ratio of X chromosomes to autosomes (Madl and Herman 1978). This signal appears to regulate the activity of seven genes which, in turn, regulate the sexual phenotype. The mutant phenotypes of these seven genes are summarized in Table 1. A loss-of-function (lf) mutation of any of these seven global sex determination genes has a dramatic effect on the sexual differentiation of most or all tissues of *C. elegans*. Thus, XX animals homozygous for a null mutation in any of the three *tra* genes develop along the male pathway of development, whereas the development of XO animals is unaffected (Hodgkin and Brenner 1977). Since the absence of any of the *tra* products leads to this phenotype, the wild-type function of the three *tra* genes must normally be required for the development of XX animals as hermaphrodites. Conversely, both XX and XO animals homozygous for a loss-of-function mutation in any of three *fem* genes are feminized (Nelson et al. 1978; Kimble et al. 1984; Donaich and Hodgkin 1984; Hodgkin 1986). The feminized XX animal

Table 1. Global sex determination genes in *C. elegans*

Gene	Loss-of-function mutant phenotype			
	XX		XO	
	Soma	Germ line	Soma	Germ line
Wild type	Female	Sperm, oocytes	Male	Sperm
fem-1	Female	Oocytes	Female	Oocytes
fem-2	Female	Oocytes	Female	Oocytes
fem-3	Female	Oocytes	Female	Oocytes
tra-1	Male	Sperm, oocytes	Male	Sperm, oocytes
tra-2	Pseudomale	Sperm	Male	Sperm
tra-3	Pseudomale	Sperm, oocytes	Male	Sperm
her-1	Female	Sperm, oocytes	Female	Sperm, oocytes

no longer makes sperm, but somatically, it is identical to a hermaphrodite XX animal. Thus, based on the same reasoning as used for the *tra* genes, the wild-type gene products of each of the *fem* genes must be necessary for normal male development –both in the somatic tissues and in the germ line. Finally, XO animals homozygous for a recessive mutation of *her-1* develop as hermaphrodites, whereas XX *her-1* animals remain unaffected (Hodgkin 1980). The wild-type *her-1* gene product must therefore be required for male development in XO, but not in XX animals.

Dominant gain-of-function (gf) alleles have been isolated for four of the seven global sex-determining genes described above (Hodgkin 1983 a; Trent et al. 1983; Barton et al. 1987; Doniach 1986). In all four cases, the effect on sexual phenotype of a gain-of-function mutation is opposite to the effect of a loss-of-function mutation at the same locus. Thus, for example, a loss-of-function allele of *her-1* "hermaphroditizes" XO animals, whereas a gain-of-function allele of *her-1* masculinizes XX animals (Trent et al. 1983). The finding that gain-of-function and loss-of-function alleles confer opposite phenotypes supports the idea that these genes are central to the determination of the sexual phenotype.

The epistatic relationships observed in strains harboring more than one sex determination mutation have led to a formal model of genetic regulation of sex determination (Hodgkin 1986). Figure 2 shows a simplified version of the proposed genetic pathway as it pertains to control of the sexual phenotype in somatic tissues. This pathway consists of a cascade of negative regulators that ultimately controls the state of activity of a single gene, *tra-1*. Although gene activity is indicated as ON or OFF, this is a genetic formalism and is not meant to imply a molecular mechanism of regulation. The temperature-sensitive periods of the sex determination genes for which temperature-sensitive alleles have been isolated concur with this suggested order (Hodgkin 1983 b).

The role of *tra-1* as the primary sex-determining gene in the somatic tissues (Fig. 2) is based on the finding that the somatic mutant phenotype of *tra-1* is epistatic to the mutant phenotypes of all of the other sex-determining genes (Hodgkin 1980). This result suggests that the state of *tra-1* dictates the sexual phenotype

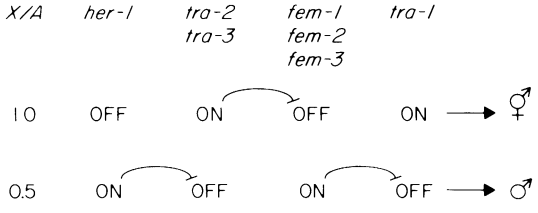

Fig. 2. Simplified pathway of genetic control of sexual determination in the somatic tissues. To achieve hermaphrodite somatic development, *tra-2* and *tra-3* negatively regulate the *fem* genes resulting in activity of *tra-1*, the gene proposed to direct hermaphrodite (female) somatic development. To achieve male development, the ratio of X chromosomes to autosomes triggers the activity of *her-1* to negatively regulate *tra-2* and *tra-3*; therefore, the *fem* genes are active and they, in turn, can negatively regulate *tra-1*. The level at which this negative regulation is executed, e. g., transcriptional, posttranscriptional, is not known. (See Hodgkin 1986 for his most recent model)

of the soma. In the germ line, the primary sex-determining genes appear to be the *fem* genes. Thus, the mutant phenotype of any of the *fem* genes is epistatic to that of the other mutations in the germ line tissue. This means that an animal homozygous for loss-of-function mutations in both *fem-1* and *tra-1*, for example, are male somatically since the *tra-1* phenotype is epistatic there, but it is female in the germ line since the *fem-1* phenotype is epistatic in this tissue (Doniach and Hodgkin 1984). The role of *tra-1* in the germ line is not understood. The null phenotype of *tra-1*, though clear in the soma (Hodgkin 1983a) is elusive in the germ line (Kimble and Schedl 1987). The *tra-1* gene may encode a single function that is specific to somatic tissues, or it may be more complex, encoding multiple products or a product with diverse functions that depend on the site of action.

3 Control of the Sperm/Oocyte Decision

In my laboratory, we have chosen to analyze sex determination in a single tissue – the germ line. Our decision to study a single tissue stems from the differences observed in the effect of mutations of the global sex determination on the sexual phenotype of the germ line vs the somatic tissues. Our decision to focus on the germ line is based on the relative simplicity of the sperm/oocyte decision compared to the formation of complex sex-specific somatic organs, on the genetic selections available for germ line sex determination mutants, and on the ability to microinject the syncytial germ line for bioassays once regulatory molecules have been isolated biochemically (Kimble et al. 1982).

3.1 Influence of Cell Ancestry on the Sperm/Oocyte Decision

Several lines of evidence suggest that the exact lineal descent of a germline cell from its progenitor, P_4, is not critical to its differentiation as either sperm or oocyte. First, in direct contrast to the development of somatic structures, where cell ancestry is critical to a cell's fate, the cell division pattern of the germ line is variable (Kimble and Hirsh 1979). Second, wild-type cells that would normally give rise to oocytes can differentiate as sperm instead (after laser ablation of the distal tip cells, Kimble and White 1981). These experiments indicate that no precursor cell that is destined to generate oocytes is set aside early in development. Third, the kind of gamete produced by the hermaphrodite germ line can be switched from spermatogenesis to oogenesis or from oogenesis to spermatogenesis by a simple temperature shift during adulthood in animals carrying a gain-of-function allele of *fem-3* (Barton et al. 1987). This last result suggests that sex determination in the germ line is a continuing process. Thus, germ line precursor cells are not committed during early development to generate either sperm or oocyte descendants. Indeed, at least some germ line cells remain uncommitted even in the adult animal.

3.2 Influence of Chromosomal Sex on the Sperm/Oocyte Decision

Both sperm and oocytes can be made by either XX or XO cells. In wild-type animals, oocytes are produced by XX cells and sperm are made by either XX or XO cells. In various mutant strains, functional oocytes are made by XO germ cells [e.g., *her-1*, Hodgkin 1980; *tra-1*(gf), Hodgkin 1983 a]. Thus, the chromosome sex of a germ cell does not prevent its differentiation as either sperm or oocyte.

3.3 Influence of the Soma on the Sperm/Oocyte Decision

The soma does not seem to be crucial to specification of a germ cell as sperm or oocyte. The wild-type female (hermaphrodite) produces both sperm and oocytes. Certain mutant hermaphrodites can produce only oocytes (see Tables 1 and 2) and others produce only sperm [see Table 2, see also below, *fem-3(gf)*] in a morphologically normal XX hermaphrodite soma. Conversely, certain mutant males (see Table 2) make germ cells that resemble oocytes in a morphologically normal male soma. Such oocyte-like cells are large and blocky in comparison to the tiny amoeboid sperm, and they contain oocyte-like granules.

Furthermore, in both hermaphrodites and males, all somatic structures (e.g., seminal vesicle, uterus) can be deleted by laser ablation of a few somatic precursor cells during L1 without blocking the initiation of sperm or oocyte formation (Kimble and White 1981). The distal tip cells must remain intact, presumably to permit sufficient proliferation of the germ line that makes both sperm and oocytes.

Although somatic structures are not required for the onset of spermatogenesis or oogenesis, hermaphrodite structures are necessary for the normal maturation of a germ cell into a functional oocyte. The oocytes produced either in a hermaphrodite gonad lacking somatic structures, or in a male gonad, are generally smaller and more irregularly shaped than normal. Thus, the hermaphrodite oviduct that surrounds maturing oocytes may be critical to normal oocyte morphogenesis.

Table 2. Germ line-specific sex determination genes in *C. elegans*

Gene	Loss-of-function mutant phenotype	
	XX	XO
Wild type	Sperm, oocytes	Sperm
fog-1	Oocytes	Oocytes
fog-2	Oocytes	Sperm
fog(*q*126)*I*	Oocytes	Sperm, oocytes
mog-1	Sperm	Sperm
mog-2	Sperm	Sperm

3.4 Genetics of Sex Determination in the Germ Line Tissue

Germ cells are directed to differentiate as either sperm or oocyte by a small number of control genes. These genes fall into two classes. The global sex determination genes, as described above, influence the specification of the sexual phenotype of all tissues in the animal, including both somatic and germ line tissues. In addition, germ line-specific sex determination genes exist that influence the choice of sexual phenotype in germ cells. The latter class includes *fog* genes, for *f*eminization *o*f the *g*erm line, and *mog* genes, for *m*asculinization *o*f the *g*erm line. The *fog* and *mog* genes and their mutant phenotypes are summarized in Table 2.

3.4.1 Selections and Screens for Mutations that Sexually Transform the Germ Line

We have devised genetic selections to isolate mutations that sexually transform the germ line (Kimble et al. 1986). The idea behind these genetic selections is simple. Basically, an XX hermaphrodite is self-sterile if it produces only sperm or only oocytes, but it is self-fertile if sperm and then oocytes are made. Therefore, mutants that feminize the hermaphrodite germ line so that only oocytes are made (or masculinize it so that only sperm are made) can be used to select for suppressor mutations that reinstate self-fertility. Selection of both masculinizing and feminizing suppressors has proved successful for isolation of dominant and/or recessive mutations both in genes that were previously known (*fem-1, fem-2, fem-3, tra-1, tra-2*) and in novel genes [*fog-1, fog-2, sup(q62), sup(q80), sup(q81)*] (Kimble et al. 1986; Kimble laboratory, unpublished results).

In addition to the use of genetic selections, we have conducted simple mutagenesis screens to isolate mutations that sexually transform the germ line. These screens have been done to complement the genetic selections described above in an attempt to identify all the genes that can mutate to a Fog or Mog phenotype. The progeny of approximately 8000 F1 clones have been examined for mutations that cause sexual transformation of the germ line (Maples and Kimble, unpublished). Mutations in several *fog* and *mog* genes have been isolated by this screening procedure: *fog-1(I), fog-2(V), fog(q157)II, fog(q163)III, mog-1(III)*, and *mog-2(II)*.

3.4.2 Global Sex Determination Genes with Germ Line-Specific Controls

Gain-of-function alleles of two global sex determination genes, *fem-3* (Barton et al. 1986) and *tra-2* (Doniach 1986), cause sexual transformation of the hermaphrodite germ line without affecting its soma. Neither affects the XO male sexual phenotype. A *fem-3(gf)* hermaphrodite makes sperm but no oocytes and is therefore Mog; a *tra-2(gf)* hermaphrodite makes oocytes but no sperm and is therefore female. Loss-of-function alleles of either *fem-3* or *tra-2* cause sexual transformation of both soma and germ line.

The activity of *fem-3* appears to be under at least two controls in wild-type hermaphrodites (Barton et al. 1987). First, in wild-type hermaphrodites, the influence of *fem-3* is limited to the germ line; spermatogenesis, a *fem-3*-dependent male process, occurs without masculinization of the female (hermaphrodite) soma. In *fem(gf)* hermaphrodites, like in wild-type hermaphrodites, mesculinization is confined to the germ line. One simple mechanism for this tissue-specific limitation might be that *fem-3* is produced in the germ line and not in the soma. Alternative possibilities include the activation of *fem-3* late in development, at a time when the somatic sex has been determined, a lower threshold for action of *fem-3* in the germ line compared to the soma, or tissue-specific regulation of another gene (or its product) upon which the activity of *fem-3* depends.

Second, in wild-type hermaphrodites, although the activity of *fem-3* is necessary for spermatogenesis, it must be regulated to permit the onset of oogenesis. In *fem-3(gf)* hermaphrodites, sperm are made continuously and in vast excess (Barton et al. 1987). A likely explanation of the defect resulting in this mutant phenotype is that the *fem-3(gf)* gene, or its product, is no longer sensitive to a negative control that is normally imposed to begin oogenesis. A negative regulation of *fem-3* activity is also implied by the maternal effects observed for *fem-3(lf)* mutants (Hodgkin 1986; Barton et al. 1986). If *fem-3* is produced in oocytes for sex determination in the embryo, then the product packaged in the oocyte must be in an inactive form, otherwise, the oocyte might have been transformed into a sperm. The inactivation of *fem-3* in the oocyte must be reversible if *fem-3* is to function during embryogenesis. Thus, negative regulation of *fem-3* activity is suggested both to permit the onset of oogenesis and to permit packaging of *fem-3* into oocytes.

The wild-type activity of *tra-2* is required for both somatic development and the production of oocytes in hermaphrodites (Hodgkin 1980). Thus, in XX animals, *tra-2* influences the sexual phenotype of all tissues. However, since the wild-type *tra-2* gene feminizes the germ line, that activity must be modulated to permit spermatogenesis in hermaphrodites. In *tra-2(gf)* hermaphrodites, no sperm are produced (Doniach 1986). This defect may be caused by a loss of sensitivity of the *tra-2(gf)* gene, or its product, to a negative control that is normally imposed to allow spermatogenesis (Doniach 1986). As described below, a good candidate for the negative regulator of *tra-2* is *fog-2* (Schedl and Kimble, manuscript in preparation).

3.4.3 Germ Line-Specific Sex Determination Genes

Mutations in *fog* or *mog* genes result in a transformation of cell fate. Germ cells that would normally undergo spermatogenesis in wild-type animals undergo oogenesis in *fog* mutants. Similarly, germ cells that would normally undergo oogenesis in wild-type animals undergo spermatogenesis in *mog* mutants. In XX animals, *fog* and *fem* mutants are identical. However, in XO animals, *fog* mutants are never feminized in the soma, whereas *fem* mutants are feminized in both soma and germ line. Therefore, the Fog phenotype is distinct from the Fem phenotype.

One *fog* gene, *fog-2,* has been characterized more than the others (Schedl and Kimble, manuscript in preparation). XX animals homozygous for any of eleven mutations in *fog-2* are female, whereas XO animals are male. The *fog-2* alleles are all recessive. Though none is an amber allele, they arise after EMS mutagenesis at a frequency typical of loss-of-function mutations in other genes, and they all have the same mutant phenotype. This suggests that these mutations cause a loss of the *fog-2* product.

The *fog-2* gene is not required for spermatogenesis *per se* since male spermatogenesis is not affected. Instead, *fog-2* is required for hermaphrodite spermatogenesis specifically. To determine how *fog-2* influences spermatogenesis in hermaphrodites, strains mutant at both *fog-2* and one of the other sex determination loci have been examined. The *tra-2;fog-2* double-mutant phenotype is identical to the *tra-2* null phenotype: sperm are produced continuously in the germ line (Schedl and Kimble, manuscript in preparation). The *fog-2;her-1* double-mutant phenotype is identical in XO animals to the mutant phenotype of *fog-2* in XX animals: XO hermaphrodites make no sperm. These experiments suggest that *fog-2* may be a negative regulator of *tra-2*, and provide evidence that *fog-2* is required for the onset of spermatogenesis in hermaphrodites, whether XX or XO. The gain-of-function phenotype of *tra-2* is identical to the loss-of-function phenotype of *fog-2*. If *fog-2* negatively regulates *tra-2*, then *tra-2(gf)* may be defective in regulation by *fog-2*. This possibility predicts that *tra-2(gf)* and *fog-2(lf)* mutations should behave identically in genetic tests and that the effects of *tra-2(gf)* and *fog-2(lf)* mutations should not be additive. These predictions are currently being tested.

Two other *fog* genes, *fog-1* (Hodgkin et al. 1985; Barton and Kimble, unpublished) and *fog(q126)* (Schedl and Kimble, unpublished), are required for spermatogenesis in both XX hermaphrodites and XO males. Mutation of either gene causes feminization of the germ line of both hermaphrodites and males. The null phenotype of neither *fog-1* nor *fog(q126)* has been established. Recently, numerous alleles of *fog-1* have been isolated as dominant suppressors of *fem-3(gf)* (Barton and Kimble, unpublished). The rapid isolation of many alleles of this gene should therefore provide information on its null phenotype.

Mutation of either of two *mog* genes results in the production of excess sperm with no signs of oogenesis in the XX hermaphrodite gonad (Schedl and Kimble, unpublished results). The *mog* genes have no effect on the sexual phenotype of the somatic tissue of either XX or XO animals. Unlike *fog* mutants, which make oocytes and therefore are cross-fertile, homozygous *mog* mutants are self- and cross-sterile. Genetically, the *mog* mutants are therefore more difficult to manipulate and have lagged behind the *fog* mutants in their characterization.

4 Conclusions

The exact lineal descent of a germ cell does not direct its differentiation as a sperm or oocyte in the nematode, *C. elegans*. Similarly, neither chromosomal sex nor influences from somatic tissues appear to direct the decision between sper-

matogenesis and oogenesis. However, two classes of genes are involved in this control. The global sex determination genes affect the sexual phenotype in all tissues, including both somatic and germ line tissues. Two of the global sex determination genes (*fem-3* and *tra-2*) appear to be specifically regulated to achieve the switch from spermatogenesis to oogenesis typical of hermaphrodites. In addition, there are at least five germ line-specific sex determination genes that affect the decision between spermatogenesis and oogenesis specifically.

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