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Equality for X Chromosomes

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In many species, females possess two X chromosomes and males have one X chromosome. This difference is critical for the initial determination of sex. However, the X encodes many functions required equally in males and females; thus, X chromosome expression must be adjusted to compensate for the difference in dosage between the sexes. Distinct dosage compensation mechanisms have evolved in different species. A common theme in the *Drosophila melanogaster* and *Caenorhabditis elegans* systems is that a subtle alteration of chromatin structure may impose this modest, but vital adjustment of the X chromosome transcription level.

Dosage Compensation in *Drosophila*

The predominant dosage compensation mechanism in *Drosophila melanogaster* is hypertranscription of the single male X chromosome in order to achieve an activity equal to that of both female X's (reviewed in *1*). Genetic analyses have identified four genes that are required exclusively for male viability and whose products mediate hypertranscription of the male X chromosome. These genes—*male specific lethal-1*, *-2*, *-3*, and *maleless* (*msl-1*, *-2*, *-3*, and *mle*, collectively called the *msls*)—have been characterized at the molecular level. Antibodies to any one of the MSL proteins specifically recognize hundreds of sites along the male polytene X chromosome (*2–7*). The *msl* mutants display similar phenotypes, and the proteins colocalize on the X chromosome, suggesting that they act in a heteromeric complex. Furthermore, each of the MSL proteins must be functional in order to observe the wild-type chromatin-binding pattern of the remaining three (reviewed in *1*). Direct evidence for a physical interaction between the MSLs has been demonstrated by coimmunoprecipitation of MSL-1 and MSL-2 (*6*).

The biochemical function of the putative MSL protein complex is not understood, but it may function in histone modification. Male X chromatin is highly enriched for an isoform of histone H4 monoacetylated at lysine-16 (H4Ac16) (*8*). Mutation of the corresponding lysine of yeast histone H4 produces altered transcription of several genes (reviewed in *9*). Although the mechanism of altered gene expression is not understood, neutralizing a key positive charge on the NH_2-terminal histone H4 tail may allow greater access of the transcriptional machinery to DNA (*9*). The MSL banding pattern is highly similar to that of H4Ac16, and mutation in any of the *msl* genes prevents accumulation of H4Ac16 on the male X chromosome (*10*). Perhaps one component of the MSL complex is a histone acetyltransferase or an inhibitor of a histone deacetylase.

Sequence analysis shows that MSL-1 and -3 are unlike any previously reported protein (*3*, *4*); MSL-2 contains a zinc-binding motif called the RING finger (*5–7*), and MLE is closely related to human RNA helicase A (*11*). The finding that MSL-2 contains a RING finger present in several other chromatin-binding proteins has led to the suggestion that this subunit provides the recognition specificity to distinguish the X chromosome from the autosomes (*5–7*). Mutations in the RING finger destroy *msl-2* activity (*5*), but so far no RING finger protein has been shown to possess sequence-specific DNA-binding activity (*12*). Two members of this family from *Drosophila* are *Posterior sex combs (Psc)* and *suppressor of zeste 2 [su(z)2]*, which both function in the maintenance of repressive chromatin structure in discrete regions of the genome (*13*).

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One of the more perplexing discoveries is that the MLE protein is likely to act on an RNA substrate. Not only is MLE highly similar to an RNA helicase over its entire length (*11*), but it contains two domains near its NH_2-terminus thought to bind double-stranded RNA (*14*). The glycine-rich heptad repeat near the COOH-terminus may provide another RNA-binding domain. Furthermore, ribonuclease treatment strips MLE protein from polytene chromosomes, whereas it leaves MSL-1, -2, and RNA polymerase bound (*15*). The identity of the RNA substrate or substrates of MLE is not known.

An alternative model for dosage compensation in *Drosophila* is that the autosomal rather than the X-linked genes are subject to differential expression in males and females (*16*). The most compelling argument against this idea is that the MSL proteins display male-specific binding to hundreds of sites along the X, but to very few sites on the autosomes.

Sex-Specific Regulation Through 3′ and 5′ Untranslated Regions

The X to autosome ratio (X:A) controls *Sex lethal* (*Sxl*), the master regulator of both sexually dimorphic development and dosage compensation (reviewed in *17*). Females (X:A = 1.0) make SXL protein, which represses the *msl* pathway and results in basal transcription of both X chromosomes. Males (X:A = 0.5) lack SXL protein, leaving the *msl* pathway active for hypertranscription of most X-linked genes. SXL is an RNA-binding protein that regulates alternative splicing of target transcripts in the sex determination pathway (*18*, *19*).

Characterization of the *msl-2* gene has illuminated how *Sxl* may restrict MSL function to males. Although *mle*, *msl-1*, and *msl-3* produce the same transcripts in both sexes, *msl-2* RNA is alternatively spliced in males and females (*5*). A small intron is removed from the 5′ untranslated region (UTR) of male transcripts but retained in female transcripts. SXL protein is likely to directly control alternative splicing of this intron because consensus SXL-binding sequences [poly(U)] are located adjacent to both the 5′ and 3′ splice sites (Fig. 1). Female cells that are mutant for *Sxl* splice the 5′ intron (*7*) and derepress *msl-2* translation (*6*), further supporting the idea that *msl-2* is a direct target of *Sxl*.

The two other well-characterized targets of *Sxl* regulation, *Sxl* itself and *tra*, are spliced in females to generate productive open reading frames (Fig. 1). The default male splicing pattern introduces a premature stop codon in both transcripts (*18*, *19*). The sex-specific alternative splice of *msl-2* RNA does not affect the open reading frame, yet MSL-2 protein is readily detectable in males but absent in females (*5*–*7*). It is unclear how translation of the female *msl-2* RNA is blocked. There are additional potential SXL-binding sites in the 3′ UTR, deletion of which causes partial derepression of *msl-2* in females (*7*). Similar sites are found in the 3′ UTR of some *msl-1* transcripts and may also contribute to its down-regulation in females (*3*, *20*). The presence of SXL-binding sites in both the 5′ and 3′ UTRs of female *msl-2* transcripts suggests that translation might be directly influenced by SXL protein sequestering the target RNA in the nucleus or preventing association with ribosomes. Alternatively, SXL may indirectly affect translation by blocking the removal of a negative regulatory element located in the 5′ intron.

Ectopic expression of MSL-2 protein in otherwise wild-type females is sufficient to assemble all of the known dosage compensation components onto both female X chromosomes and result in the more diffuse X chromatin structure normally found only in males (*6*). Such females suffer decreased viability, and surviving females show delayed development and poor fertility. The fact that dosage compensation components can assemble on female X chromosomes when only MSL-2 is abnormally expressed further supports the idea that *msl-2* is the primary target of *Sxl* repression in females. Whereas the other MSL proteins are synthesized in wild-type females, they are either unstable or unable to assemble onto the X chromosomes in the absence of MSL-2 (*4*, *6*, *20*, *21*).

A Second Dosage Compensation Pathway May Operate in Females

Several observations indicate that flies use a second mode of dosage compensation. *Sxl* mutant female embryos die, at least in part because the *msl* pathway is derepressed, but *Sxl*;*msl* double mutants still die (*22*, *23*). A second pathway controlled by *Sxl*, but independent of the *msl* genes, would explain this result (*24*). In support of this model, *runt*, an X-linked gene expressed early in embryogenesis, is regulated by an *Sxl*-dependent, but *msl*-independent, mechanism (*25*). Hence, *Sxl* must either directly or indirectly control a second dosage compensation pathway that is active soon after zygotic transcription begins.

The finding that SXL protein might regulate the translation of *msl-2* (and possibly *msl-1*) has prompted consideration of a direct dosage compensation model, in which SXL down-regulates translation or stability of X-encoded RNAs in females without affecting splicing. Inspection of the *runt* sequence showed that it also contains a cluster of three potential SXL-binding sites in its 3′ UTR. A further search of the *Drosophila* sequence database for transcripts with clusters of SXL-binding sites (U_8 or AU_7) in their 3′ UTRs revealed that most genes with such an organization map to the X chromosome (*6*). The exceptions support the rule, as the only known autosomal genes with clustered SXL-binding sites in their 3′ UTRs are *msl-1* and *msl-2*.

The hypothetical direct *Sxl* pathway differs from the *msl* dosage compensation pathway in several critical respects. The *msl* mechanism increases transcription in males, possibly by altering chromatin structure, whereas the direct *Sxl* pathway reduces translation or RNA stability in females. It is thought that the two dosage compensation pathways act in parallel during development (*26*, *27*). Hence, the *Drosophila* X chromosome may be interspersed with many genes that are up-regulated in males, some that are down-regulated in females, and a few that are not dosage compensated.

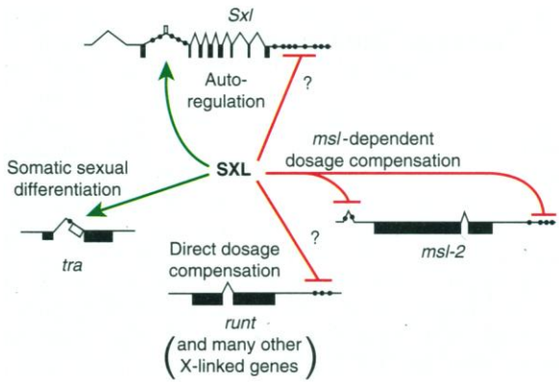

Fig. 1. Functions of the *Drosophila* SXL protein. SXL regulates somatic sexual differentiation in females by controlling the splicing of *tra* RNA (*19*). SXL is required for maintenance of the female state by positively autoregulating its own expression at the level of RNA splicing (*18*). The presence of many copies of poly(U) in the 3′ UTRs of some *Sxl* transcripts raises the possibility that SXL might also negatively regulate its own translation (*6*). SXL may repress *msl*-dependent dosage compensation in females by binding to poly(U) clusters in the untranslated regions of *msl-2* RNA (*5*–*7*). SXL may directly control a second dosage compensation pathway that acts in females to reduce expression of a subset of X-encoded transcripts, such as *runt*, that contain poly(U) clusters in their 3′ UTRs (*6*). The target transcripts are schematically shown with noncoding regions as horizontal lines, coding exons as filled boxes, exons with stop codons as open boxes, introns as bent lines, and poly(U) sites as filled circles. Green arrows indicate a positive regulatory function, and red bars indicate a postulated negative regulatory role. *Sxl* also plays a role in female germline development.

Dosage Compensation in *Caenorhabditis elegans*

In C. *elegans*, XX animals are hermaphrodites and XO animals are males. In contrast to *Drosophila*, transcription of the male X is the basal state, and transcription of both X chromosomes in the hermaphrodite is reduced by approximately 50% to achieve this level (reviewed in *28*). This strategy for dosage compensation is complementary to the *msl* pathway in *Drosophila*, but faces the same conceptual difficulty: How may a twofold difference in gene expression be imposed on the diverse mechanisms controlling the genes on a whole chromosome? As in *Drosophila*, this is achieved by the action of one or more X chromosome–associated proteins that act in a sex-specific manner (*29*).

The genes required in hermaphrodites can be divided into two groups (Fig. 2): (i) genes that affect both sex determination and dosage compensation (*sdc* genes), and (ii) genes that affect only dosage compensation (*dpy* or *dumpy* genes). All of these—*sdc-1*, *sdc-2*, *sdc-3*, *dpy-21*, *dpy-26*, *dpy-27*, *dpy-28*, and *dpy-30*—are required for reduction of X-linked gene expression in hermaphrodites (reviewed in *28*). In general, loss of both maternal and zygotic contributions of wild-type *sdc* or *dpy* functions results in XX inviability. Escapers, or animals lacking only the zygotic functions of these genes, have a dumpy phenotype: They have short, fat bodies and are egg-laying defective. Notable exceptions are *sdc-2*, which requires zygotic function for viability (*30*), and *sdc-1* and *dpy-21*, which display weaker effects on viability than the others (*31*, *32*).

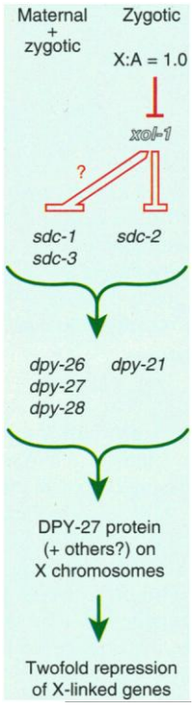

Fig. 2. The *C. elegans* dosage compensation regulatory hierarchy drawn from the perspective of the XX hermaphrodite. Genes on the left have both maternal and zygotic components, and genes on the right function zygotically. The X:A ratio is the primary determinant of sex. When the ratio is 1.0, the earliest known gene in the pathway, *xol-1*, is repressed. This results in zygotic activation of *sdc-2* and function of all the *sdc* and *dpy* gene products to repress X-linked transcription twofold. It is not yet known which components may directly associate with the X, like DPY-27, and which products regulate this event. The *sdc* genes are placed upstream in the hierarchy based on their additional role in sex determination. *dpy-30* is not placed in the hierarchy because its position is currently under reevaluation (*49*). Green arrows represent positive interactions and red bars depict negative regulation. The open red bars indicate that *xol-1* repression of the *sdc* genes does not occur in the hermaphrodite.

The simplest position for the *sdc* genes in the genetic hierarchy is in a common regulatory pathway leading to independent sex determination and dosage compensation branches. *sdc-1* encodes a 139-kD protein with seven TFIIIA-like zinc finger motifs, suggesting that it functions in gene regulation (*33*). *sdc-2* (*34*) may be a direct target of the first known gene in the hierarchy, *xol-1* (*35*). SDC-3 regulates sex determination and dosage compensation through independent domains (*36*, *37*). Sex determination–specific mutations affect an apparent adenosine triphosphate (ATP)–binding domain, whereas dosage compensation–specific mutations affect a pair of zinc finger motifs. The presence of putative DNA-binding motifs in both SDC-1 and SDC-3 is compatible with a positive regulatory effect on the *dpy* genes (Fig. 2). Alternatively, one or more of the SDC proteins could participate more directly in repression of the X chromosome.

The dosage compensation–specific DPY proteins are most likely direct regulators of the X chromosome. This is the case for DPY-27, which is associated with the X chromosomes in hermaphrodites but not in males, starting at the 30-cell stage of embryogenesis (*29*). The association of DPY-27 protein with the X chromosomes in hermaphrodites provides strong evidence that the prevailing model for C. *elegans* dosage compensation is correct; the mechanism operates by decreasing gene expression in hermaphrodites rather than increasing gene expression in males. Furthermore, the DPY-27 sequence provides support for a model in which dosage compensation is achieved through regulation of higher order chromosome structure (*29*). DPY-27 is a member of the SMC family of proteins (reviewed in *38*), which are involved in several aspects of chromosome dynamics, including chromosome condensation in *Xenopus* extracts (*39*) and chromosome segregation in budding and fission yeast (*40*). Members of this family are characterized by an NH_2-terminal ATP-binding motif, a conserved COOH-terminal domain, and a central coiled-coil region reminiscent of motor proteins such as myosin or kinesin. The ATP-binding motif in DPY-27 is essential for its function (*29*), consistent with a model in which regulation of chromosome structure by SMC proteins is energy dependent (*38*). The homology to proteins required for general chromosome segregation of yeast fits well with a previously established link between chromosome behavior and dosage compensation: *dpy-26* and *dpy-28* mutants (but not *dpy-27*) have a nondisjunction phenotype (*32*, *41*). DPY-27 protein, and perhaps other factors required for X chromosome dosage compensation in C. *elegans*, may be specialized versions of proteins that regulate general chromosome function in many organisms. Some part of *dpy-30* function is indeed general, as mutations affect the development and morphology of both sexes (*42*). Consistent with this phenotype, *dpy-30* encodes a 123–amino acid nuclear protein present in both sexes at all stages of development (*43*).

The Sex Specificity of X Chromosome Repression

The *sdc* and *dpy* genes are members of a genetic hierarchy that responds to the X:A ratio in the zygote (Fig. 2) (reviewed in *28*). When the X:A ratio is 0.5 (male), the *xol-1* (XO lethal) gene represses function of the *sdc* and *dpy* genes (*44*). When the X:A ratio is 1.0 (hermaphrodite), *xol-1* is inactive, the *sdc* and *dpy* genes are functional, and dosage compensation occurs. However, most of the *sdc* and *dpy* genes have significant maternal contributions, suggesting that sex specificity is not strictly determined by zygotic activation of these genes in response to the X:A ratio (*28*). In addition, although the DPY-27 protein is associated with the X chromosomes only in hermaphrodites, it is present in the male nucleus, indicating that regulation does not occur at the level of its synthesis (*29*). As with *Drosophila msl* gene products, the continued expression, stability, or localization of maternally supplied dosage compensation regulators might be regulated by a gene with strict zygotic function, analogous to *msl-2*. The best candidate in C. *elegans*, based on its essential zygotic component, is *sdc-2* (Fig. 2) (*30*). Expression of *sdc-2* is thought to be directly repressed by *xol-1* in males, which in turn is zygotically expressed in response to the X:A ratio (*35*).

Sex-specific regulation of *xol-1* promises to shed light on how the X:A ratio is measured, as *xol-1* may be the direct target of the primary sex determination and dosage compensation signal (*35*). At the peak of its expression, *xol-1* RNA is approximately 10 times more abundant in males than in hermaphrodites. An *xol-1–lacZ* translational fusion (*35*) and an analogous transcriptional fusion (*45*) exhibit XO-specific β-galactosidase expression in embryos, suggesting that some component of the X:A ratio acts through the *xol-1* promoter. The identity of X:A numerator and denominator elements and further analysis of the sex-specific regulatory elements of *xol-1* should be extremely informative as to the molecular mechanism for X:A measurement (*35*, *46*).

It is still an open question whether the C.

elegans X chromosome is dosage compensated on a gene by gene basis, as the *Drosophila* X appears to be, or by a long-range chromosomal phenomenon like X inactivation in mammals (reviewed in *1*, *47*). If the mechanism is more similar to X inactivation, then it could spread long distances to neighboring chromatin in X:A translocations. If it operates on a gene by gene basis, then X-linked genes moved to autosomes should retain dosage compensation. Data to support either of these models are scarce, in large part because of the transformation system in *C. elegans*, in which microinjected DNA is usually maintained in extrachromosomal arrays rather than within the genome in single copy. Therefore, individual X-linked genes have not been assayed for dosage compensation when inserted into autosomes (*28*). However, in an unpublished study by Hsu and Meyer (cited in *28*), an autosomal gene, *unc-54*, was dosage compensated when inserted onto the X chromosome, so in this example any hypothetical cis-acting elements must have been able to function over distances of several kilobases. In addition, in one genetic study, mutations in several autosomal loci were not fully complemented by the autosomal portion of a translocation between the X and chromosome V, suggesting that the X signals might act over long distances to repress juxtaposed chromatin (*48*). The ability to stain for DPY-27 protein on translocation chromosomes should begin to allow the resolution of this very fundamental question.

Things to Come . . .

In this review, we have highlighted aspects of X chromosome dosage compensation in two model organisms, fruitflies and nematodes. A third system that is of extreme interest to the chromosome field is the X-inactivation mechanism used by female mammals (*47*). A potentially fundamental breakthrough in that field may be forthcoming, as researchers determine whether inactivation of a whole chromosome relies, at least in part, on the expression of a nonprotein-coding RNA molecule, termed Xist, from the inactive X chromosome. We await with excitement the elucidation of this third, distinctive mechanism of X chromosome dosage compensation.

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Gametic Imprinting in Mammals

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Embryonic development in mammals is distinct from that in other vertebrates because it depends on a small number of imprinted genes that are specifically expressed from either the maternal or paternal genome. Why mammals are uniquely dependent on sexual reproduction and how this dependency is dictated at a molecular level are questions that have been intensively investigated during the past 2 years. Gene inactivation experiments have confirmed predictions that imprinted genes regulate embryonic and placental growth and that DNA methylation is part of the imprinting mechanism. Despite these considerable achievements, the reason why imprinted hemizygosity is used as a mechanism to regulate the intrauterine growth of mammalian embryos remains elusive.

In mammals some genetic traits show parental dependency and are only expressed when inherited from one parent. Two types of parental dependency are currently known. The first has a trivial cause and is due to an unequal distribution of genetic information between male and female gametes. Examples of this type include traits encoded by mitochondrial genes, Y chromosome–linked genes, and maternal-effect genes. The second type, known as gametic or genomic imprinting, is more of an enigma whose role in mammalian development and disease is not yet fully appreciated. Gametic imprinting describes those parental-dependent traits in which both the male and female allele are present but function unequally in the embryo.

Genes whose expression is restricted to either the maternal or paternal allele constitute the best known example of gametic imprinting. Sixteen such genes have been described in mice and humans, 5 of which are maternally expressed and 11 paternally expressed (Table 1). However, other traits such as trinucleotide repeat amplification, host-defense methylation responses, asynchrony of sister chromatid behavior, and meiotic recombination also exhibit parental dependency (*1*). Whether these latter traits arise from gametic imprinting is not yet clear; therefore, they will not be considered further in this brief review.

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