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Minireview

A balancing act between the X chromosome and the autosomes

Mimi K Cheng and Christine M Disteche

Address: Departments of Pathology and Medicine, University of Washington, Seattle, WA 98195, USA.

Correspondence: Christine Disteche. Email: cdistech@u.washington.edu

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Abstract

Dosage compensation equalizes gene dosage between males and females, but its role in balancing expression between the X chromosome and the autosomes may be far more important. Now, DNA microarrays have shown equality between the average expression of X-linked genes and that of autosomal genes, in male and female tissues of flies, worms and mice.

Sex chromosomes have evolved from an ordinary pair of autosomes many times, including in the lineages of flies, worms, mammals, and many others. In each case, the lack of recombination between the X and Y chromosomes led to loss and differentiation of genes on the Y chromosome, leaving males with a single copy of most X-linked genes [1]. To protect organisms against deleterious effects of this X-chromosome monosomy, mechanisms of dosage compensation evolved.

The regulated dosage of any one gene is not necessarily important for the viability of an organism, but the gene dosage of a whole chromosome, or even a part of a chromosome, is vital. In *Drosophila*, having only one copy of (being haploid for) as little as 1% of the genome reduces viability, and being haploid for more than 3% of the genome is lethal [2]. Given that the *Drosophila* X chromosome makes up about 20% of the genome, flies cannot tolerate X-chromosome deletions [2,3]; and yet *Drosophila* females have two X chromosomes whereas males only have one. How is this tolerated?

An early clue to the mechanism of dosage compensation between the sexes was found in autoradiographs of salivary gland polytene chromosomes, which showed that the single X chromosome in male flies (whose genotype can be written X;AA, where A represents an autosome) is expressed at twice the level found in females (XX;AA) [4]. A multiprotein complex termed the male-specific-lethal (MSL) complex was found to bind specifically to the male X chromosome, hyperacetylating its histone H4 at lysine 16 (H4 K16) and increasing transcription from the chromosome. In male germ cells, however, the MSL complex and H4 K16 hyperacetylation of the X chromosome are not found [5], and the MSL gene products are not required for the viability of the *Drosophila* germline [6,7]. These findings suggest that either germ cells do not need to undergo dosage compensation, or germline dosage compensation is independent of the MSL complex. The findings of Gupta *et al.* now published in *Journal of Biology* [8] indicate that the *Drosophila* germline does in fact compensate for the dosage of the X chromosome.

Gupta *et al.* [8] used microarray analysis to determine the expression of the X chromosomes and autosomes in male and female *Drosophila* soma and gonads. For the experiments

with the soma, the authors genetically manipulated the sex-determination pathway to produce sex-transformed tissues with no germline. This elegant approach allowed them to determine the X-chromosome expression dosage without the complications caused by the sexually dimorphic expression of some genes. Furthermore, they performed a series of control experiments using mutant flies to show that changing the gene dose results in a change in expression that is easily detected by microarray analyses. They determined this using stocks with either a duplication (Dp) or a deletion (Df) of chromosome arm 2L. The resulting detected gene dose changed from 1.0 to 1.5 (in the region that has three copies in *Dp*/+ flies and two in *Df*/+ flies) and from 1.0 to 3.0 (in the region that has three copies in *Dp*/+ flies and one in *Df*/+ flies).

Having validated their approach, Gupta *et al.* [8] compared expression of the X chromosome with that of the autosomes in males and females. They found that the single X chromosome of male soma and gonads was expressed at the same level as the combined two X chromosomes of female soma and gonads; that is, the expression ratios between X chromosomes and autosomes of XX;AA female soma and X;AA male soma centered on 1. These findings confirm that, in *Drosophila* somatic tissues, there is a doubling of transcription from the single male X chromosome. In the germline, however, the findings of Gupta *et al.* [8] suggest that the X chromosomes in both sexes are hypertranscribed relative to autosomes, but also that the two X chromosomes of females are repressed, as the expression ratios of not only testes (X;AA) but also XX;AA ovaries and X;AA sex-transformed ovaries all centered on 1 (Figure 1).

Microarray experiments performed by Gupta *et al.* [8] on somatic tissues from *Caenorhabditis elegans* and mouse indicate that, in those species too, the X chromosomes are hypertranscribed relative to the autosomes. In a similar set of experiments, our lab [9] used microarray analyses of multiple tissue types in several mammalian species to demonstrate that the active X chromosome in both sexes is hypertranscribed. It had been predicted that once a Y-linked gene is lost during evolution, its X-linked partner would

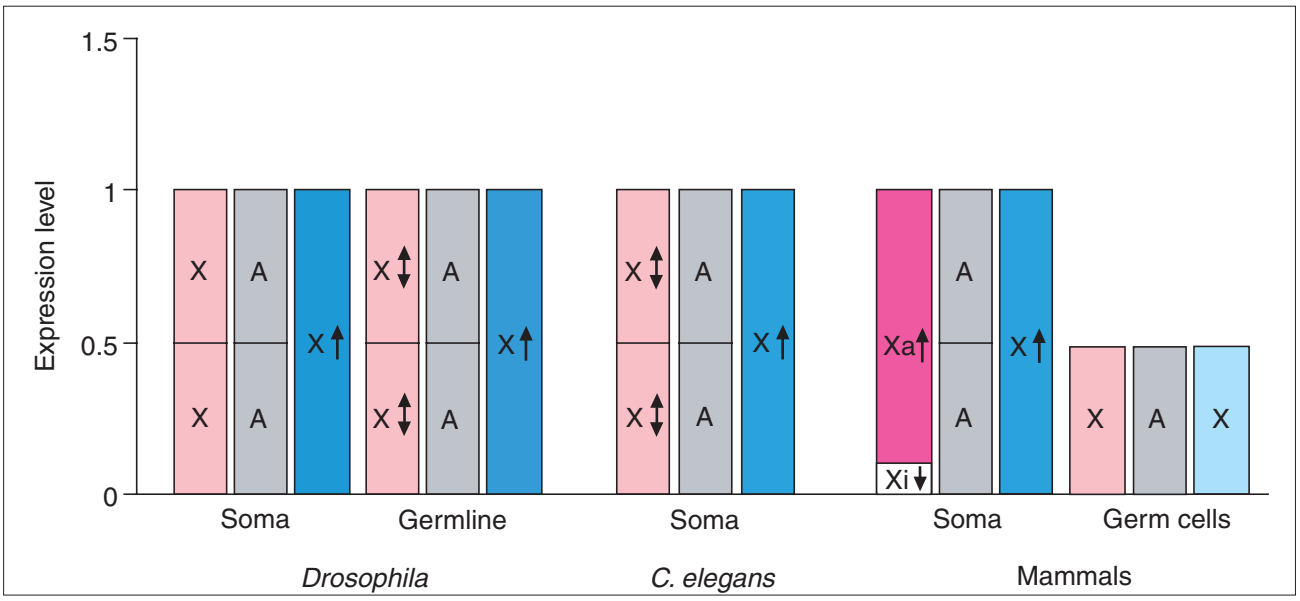

Figure 1
Dosage compensation occurs in *Drosophila*, *C. elegans*, and mammals [8,9]. If the expression level of each pair of autosomes (gray for both males and females) is set to 1.0, then the expression level of the two X chromosomes in females (pink) and the single X chromosome in males (blue) is also equal to 1.0. To achieve this dosage compensation, the single X chromosome in the *Drosophila* male soma and germline, *C. elegans* male soma, and mammalian male soma is upregulated (dark blue, up-arrow). In *Drosophila* female soma, the X chromosomes are both expressed and thus not upregulated (light pink). According to Gupta *et al.* [8], each X chromosome in the *Drosophila* female germline is probably upregulated, and yet they must also be downregulated somehow, in order to prevent functional tetrasomy (light pink, double arrow). The X chromosomes in *C. elegans* hermaphrodite soma are presumably upregulated, but they are also known to be downregulated by half (light pink, double arrow). In mammalian females, one of the two X chromosomes is active and upregulated (dark pink, up-arrow), while the other X chromosome gets inactivated (white, down-arrow). The haploid germ cells of mammals express but do not upregulate their X chromosomes to achieve the same level of autosomal expression (0.5; light pink for female and light blue for male) [9]. Primary mammalian oocytes, which have two non-upregulated X chromosomes, and spermatocytes, in which the X chromosome is largely silenced, are not depicted.

have to be hypertranscribed [1,10]. Both microarray studies [8,9] provide concrete evidence that it is indeed important for X-chromosome gene-expression dosage to be balanced with that of autosomes in all species (Figure 1). Although increased expression of the X chromosome seems the most logical and simple mechanism to equalize gene dosage between the X chromosome and the autosomes, decreased expression from all the autosomes would also result in balanced expression [11].

Perhaps the most important finding of Gupta *et al.* [8] is the fact that the X chromosomes in the *Drosophila* germline are upregulated to match the expression of the autosomes. The molecular mechanism of dosage compensation in these cells is a mystery, as there is no MSL complex in the germline. In the mammalian germline, our lab [9] found that the X chromosome was expressed but not always upregulated. But because secondary oocytes and spermatids are haploid (X;A) and primary oocytes have two active X chromosomes (XX;AA), the X chromosome would not need to be upregulated in these cells (Figure 1). Whether primary oocytes use a combination of upregulation and repression of both X chromosomes, as Gupta *et al.* [8] suggest for the *Drosophila* female germline, remains to be determined. In the mammalian male germline, upregulation of the X chromosome achieves dosage compensation in spermatogonia (XY;AA), and spermatocytes appear to be the only cell type with very low expression of the X chromosome compared with autosomes, owing to a silencing mechanism that inactivates unpaired chromosomes [9].

The finding that X-chromosome expression is upregulated in *Drosophila*, *C. elegans*, and mammals suggests that dosage compensation is essential across species. The *Drosophila* soma achieves this dosage compensation by selectively boosting expression from the male X chromosome. In contrast, mammals and *C. elegans* increase expression of the X chromosome in both males and females (or males and hermaphrodites in *C. elegans*). Then, to avoid having the X chromosome expressed at four times normal levels ('functional tetrasomy'), mammalian females silence one X chromosome by X inactivation, whereas *C. elegans* hermaphrodites decrease expression of both X chromosomes (Figure 1). Thus, mechanisms of dosage compensation differ greatly between species, probably because they evolved separately in each species out of necessity. The selective hypertranscription of the male X chromosome in the *Drosophila* soma may be related to the use of common pathways between sex determination and dosage compensation in this species.

Interestingly, the expression of the X chromosome seems to be slightly higher than that of autosomes in most *Drosophila* samples tested [8]. Perhaps the hypertranscription of the X chromosome overcompensates and another mechanism is also needed to block or repress expression in order to achieve a perfect balance between the X chromosome and the autosomes. Higher expression of the X chromosome may also have a selective advantage related to sexual reproduction, which may account for the observed increase in X-chromosome expression in mammalian brain tissues [9].

Despite obvious differences, the molecular mechanisms of upregulation of the X chromosome may ultimately have features in common between species. Upregulation may have evolved gene-by-gene, through DNA sequence modifications following loss of the Y-linked gene. Alternatively, mammals and *C. elegans* may use a multi-protein complex for dosage compensation, as seen in *Drosophila*. A combination of such processes may also be at work to modulate the expression of the X chromosome in the soma and germ cells. Further studies to elucidate how each species achieves dosage compensation between the X chromosomes and the autosomes in the soma and germline will provide insights into both the evolution of sex chromosomes and the mechanisms of chromosome-wide gene regulation.

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