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REVIEW

Dosage compensation and the global re-balancing of aneuploid genomes

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Abstract

Diploid genomes are exquisitely balanced systems of gene expression. The dosage-compensation systems that evolved along with monosomic sex chromosomes exemplify the intricacies of compensating for differences in gene copy number by transcriptional regulation.

Complex genomes are more than just the sum of their genes, but are rather complex regulatory systems in which the expression of each individual gene is a function of the activity of many other genes, so that the levels of their protein products are maintained within a narrow range. Such homeostasis favors the maintenance of the appropriate stoichiometry of subunits in multiprotein complexes or of components in signal transduction pathways, and defines the 'ground state' of a cell [1]. In diploid genomes, both alleles of a gene are usually active and this 'double dose' of each gene is figured into the equation. Thus, deviations from diploidy, such as the deletion or duplication of genes or of larger chromosomal fragments (aneuploidy), unbalance the finely tuned expression of the genome. Segmental aneuploidies of this kind can arise from failed or faulty repair of chromosomal damage due to irradiation, chemical insult or perturbation of replication, or from illegitimate recombination during meiosis. Loss or duplication of entire chromosomes (monosomy or trisomy, respectively) can arise from non-disjunction during cell division. Depending on the extent of the aneuploidy and on the genes affected, the fine balance of *trans*-acting factors and their chromosomal binding sites that define the gene-expression system is disturbed, and the fitness of the cell or organism challenged.

Often, aneuploidies have been associated with a variety of developmental defects and malignant aberrations, such as Down syndrome or certain breast cancers (reviewed in [2,3]). The phenotypes associated with changes in gene copy number can not only be the result of the deregulation of the affected gene(s), but may also reflect *trans*-acting effects on other chromosomal loci or even more global alterations of the entire regulatory system. This is particularly true if genes coding for regulatory factors, such as transcription factors, are affected (reviewed in [4,5]).

Strategies for re-balancing aneuploid genomes

Genome-wide studies in different organisms reveal that the expression of a substantial number of genes directly correlates with gene dose (the primary dosage effect) [6]. In other cases, the measured expression levels do not reflect the actual copy number, as compensatory mechanisms aimed at re-establishing homeostasis take effect [4,5]. Imbalances due to aneuploidy may be compensated for at any step of gene expression from transcription to protein stability. Excess subunits of multiprotein complexes that are not stabilized by appropriate interactions are susceptible to degradation (see [1] for a discussion of compensation at the protein level). Dosage-compensation mechanisms at the level of transcription are versatile, intricate, and in no instance are they fully understood.

In principle, three types of compensatory responses to aneuploidies are recognized: buffering, feedback, and feed-forward, which may act individually or, more likely, in combination [7]. Oliver and colleagues [7] define buffering as 'the passive absorption of gene dose perturbations by inherent system properties'. Currently, the nature of this general or 'autosomal' buffering is unknown, but its existence can be deduced from comparing gene expression to DNA copy number in healthy and aneuploid genomes [8-11]. The system properties referred to by Oliver and colleagues can be considered as the sum of the biochemical equilibria of the system 'living cell', which are predicted to moderate the effect of the reduction of one component. Apparently, the deletion of one gene copy (that is, a twofold reduction in gene expression) can be partially compensated for by increasing the steady-state mRNA levels originating from

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the remaining allele by, on average, 1.5-fold [7,11]. Interestingly, Stenberg and colleagues [11] observed that buffering appears to compensate for deficiencies better than for gene duplications, which leaves open the existence of a general sensor of monosomy that mediates the effect. A general buffering will also ameliorate the consequences of widespread mono-allelic gene expression due to parental imprinting (cases where a single allele is expressed, depending on whether it is inherited from the father or mother) [12].

In contrast to the general and nonspecific buffering just described, a 'feedback' mechanism would be defined as gene-specific - sensing and readjusting the levels of specific molecules by appropriate, specific mechanisms. Finally, 'feed-forward' anticipates the deviation from the norm and hence can only be at work in very special circumstances. Prominent examples where feed-forward scenarios are applicable are the widely occurring monosomies in the sex chromosomes of heterogametic organisms (for example, the XX/XY sex-chromosome system), which are present in each and every cell of the species.

In contrast to aneuploidies that arise spontaneously, these 'natural' monosomies and their associated dosage-compensation mechanisms are the products of evolution. Research on dosage-compensation mechanisms associated with sex chromosomes continues to uncover unexpected complexities and intricacies. The somatic cells of the two sexes of the main model organisms of current research - mammals, nematode worms (*Caenorhabditis elegans*) and fruit flies (*Drosophila melanogaster*) - differ in that those of females are characterized by two X chromosomes, while those of males have one X and one Y chromosome (mammals and *Drosophila*); or one sex (XX) is a hermaphrodite and the males have just a single X and no Y chromosome (X0) (*C. elegans*) [13]. Remarkably, different dosage-compensation strategies for balancing gene expression from the X chromosome between the sexes have evolved independently in these three cases (Figure 1), as we shall discuss in this article. There is increasing evidence that in all three cases, the transcription of most genes on the single male X chromosome is increased roughly twofold [14-16]. In fruit flies, this upregulation of the X chromosome is limited to males. In mammals and worms, however, the X chromosomes appear to be also upregulated in the XX sex, which necessitates additional compensatory measures. In female mammals, one of the X chromosomes is globally silenced, whereas in hermaphrodite worms, gene expression on both X chromosomes is downregulated by about 50% (Figure 1). An emerging principle is that the net fold-changes of dosage compensation are not achieved by a single mechanism (that is, there is no simple switch for 'twofold up'), but by integration of activating and repressive cues, as discussed later.

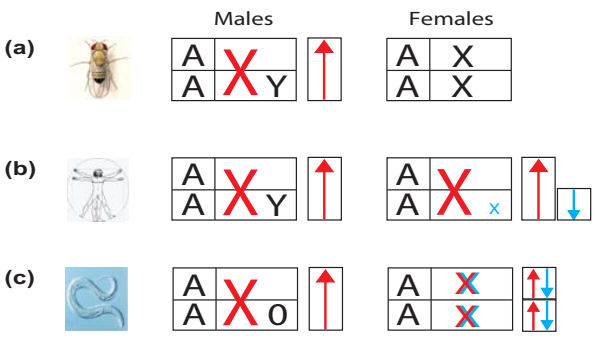


Figure 1. Schematic representation of different dosage-compensation systems. (a) *Drosophila melanogaster*, **(b)** *Homo sapiens*, **(c)** *Caenorhabditis elegans*. Combinations of chromosomes in the diploid somatic cells of males and females are shown. The sex chromosomes are symbolized by the letters X and Y, autosomes as A. Dosage-compensated chromosomes are colored: red indicates activation, blue repression. The sizes of the As indicate the average expression level of an autosome in a diploid cell. The sizes of the X chromosomes reflect their activity state (see text). The arrows represent the activating and repressive factors that determine the activity of the corresponding sex chromosome. In *Drosophila* (a), the male X chromosome is transcriptionally activated twofold in the male to match the total level of expression from the two female X chromosomes. In mammals (b), X chromosomes are hypertranscribed in both sexes, and to equalize X-chromosomal gene expression between the sexes, one of the two X chromosomes is inactivated in females. In *C. elegans* (c), males do not have a Y chromosome (O indicates its absence) and XX individuals are hermaphrodites. Worms also overexpress X-linked genes in a sex-independent manner, as indicated by the red-colored Xs, but subsequently halve the expression levels of the genes from both X chromosomes in the hermaphrodite (indicated by the blue Xs) to equalize gene dosage between the sexes.

In what follows we summarize recent insight into the dosage-compensation mechanisms of the XX/XY sex chromosome systems, which nicely illustrate the evolution of global, genome-wide regulatory strategies. However, compensation systems of this type are not absolutely required for the evolution of heterogametic sex. Birds, some reptiles, and some other species use the ZW/ZZ sex-chromosome system, which does not use the mechanism of chromosome-wide transcriptional regulation to compensate for monosomy [17-19].

Dosage compensation of sex chromosomes reveals the balancing capacity of chromatin

The sex chromosomes of the XX/XY system are thought to have originated from two identical chromosomes in a slow process that was initiated by the appearance of a male-determining gene. In order to be effective, this gene should be propagated only in males, which was achieved by evolving a Y chromosome that was specifically propagated through the male germline. The necessary suppression of recombination between this 'neo-Y' chromosome

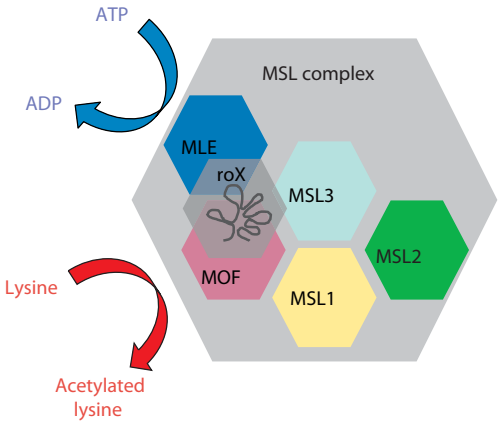
and the corresponding sister chromosome (which would become the future 'neo-X') favored the accumulation of mutations, deletions and transposon insertions, an erosive process that led to loss or severe degeneration of Y chromosomes [20-24]. The progressive erosion of the evolving Y left many X-chromosomal genes without a corresponding copy on the Y chromosome (the hemizygous state). The initial consequences of gene loss on the Y chromosome may have been absorbed by the intrinsic biochemical buffering properties of the cell noted above [11]. However, when the majority of genes on the X chromosome lost their homologs on the Y chromosome the co-evolution of regulatory processes to overcome the reduced gene dose - that is, dosage-compensation systems - increased the fitness of the organisms. These dosage-compensation systems are likely to originate in the male sex (XY or X0 in the examples discussed here), as it is in males that factors acting in a dose-dependent manner (such as transcription factors, chromatin constituents and components of signal-transduction cascades) would become limiting [25,26].

A logical adaptation to ensure the survival of males would be the increased expression of X-chromosomal genes [6]. This intuitively obvious mechanism has long been known in *Drosophila*. Observing the specialized polytene chromosomes in larvae (which are composed of thousands of synapsed chromatids arising from repeated DNA replication without chromosome segregation), Mukherjee and Beermann [27] were able to directly visualize nascent RNA and found that the single X chromosome in males gave rise to almost as much RNA as two autosomes. Recent genome-wide expression analyses confirmed these early observations [28,29] and further genome-wide studies suggest that this mechanism may also operate in *C. elegans* and mammals [14-16]. For these species neither the mechanism of this chromosome-wide regulation nor the factors involved are known.

For *Drosophila*, however, thanks to decades of outstanding genetics exploring male-specific lethality, we know at least a few of the prominent players. Here, the twofold stimulation of transcription on the X chromosome is mediated by the male-specific assembly of a dosage-compensation complex (the Male-Specific-Lethal (MSL) complex), a ribonucleoprotein complex that associates almost exclusively with the X chromosome (reviewed in [30]; Figure 2). Most subunits of the MSL complex are found in both sexes of *Drosophila*, except for the key protein MSL2 and the noncoding *roX* (RNA-on-the-X) RNAs, which are only expressed in males (Figure 2), thus leading to the assembly of the MSL complex exclusively in male cells. The MSL complex associates with the transcribed regions of target genes in a multi-step process that has been reviewed elsewhere [31-33]. Key to the stimulation of transcription is the MSL-complex subunit MOF (Males-absent-on-the-first; also known as KAT8, lysine acetyltransferase 8), a histone acetyltransferase with specificity for lysine 16 in the amino-terminal tail of histone 4 (H4K16ac). Acetylation of this residue is known to reduce interactions between nearby nucleosomes and leads to unfolding of nucleosomal fibers *in vitro* [34,35].

Whereas the action of the dosage-compensation complex in *Drosophila* is limited to males, in *C. elegans* and mammals the unknown factors that stimulate X-chromosomal transcription appear to be active in the hermaphrodite and the female, as well as in males. If, however, X activation re-balances the male genome in these species, it follows that in the XX sex, having two hyperactive X chromosomes relative to the autosomes must be suboptimal [36]. Consequently, further compensation is needed. Mammals have evolved a strategy of inactivating one of the female X chromosomes to achieve a level of X-chromosome gene expression closely resembling that from the single X in males (reviewed in [37]; Figure 1b). Which X is inactivated is random, and inactivation starts with the stable transcription of the long, non-coding *Xist* (Xi-specific transcript) and *RepA* (repeat A) RNAs from a complex genetic region on the future inactive X (Xi) called the X-inactivation center. Subsequently, *Xist* RNA - possibly in complex with undefined protein components - spreads to coat the entire Xi. Silencing involves the recruitment and action of the Polycomb silencing machinery via the *Xist* and *RepA* RNAs [38,39], followed by reinforcement through the incorporation of histone variants, removal of activating histone modifications and DNA methylation [37]. Remarkably, the independent evolution of nematode worms arrived at a very different solution to the problem. *C. elegans* equalizes the gene dose by halving the expression levels of genes on both X chromosomes in the hermaphrodite, using a large dosage-compensation complex containing components of the meiotic/mitotic condensin. The involvement of condensins may point to regulation at the level of chromatin fiber compaction ([40] and references therein). The scenario shown schematically in Figure 1c for *C. elegans* suggests that dosage compensation in this species involves a twofold increase in X-linked transcription in both sexes, which is opposed by a twofold repression in hermaphrodites. The underlying mechanisms are still mysterious.

This short summary of the three very different dosage-compensation systems reveals two common denominators. First, they all adapt factors and mechanisms, which are already involved in other regulatory processes, for the compensation task by harnessing them in a new molecular context. Furthermore, these factors are all known for their roles in modulating chromatin structure. It seems that chromatin can adopt a variety of structures



	Domain	Function
MSL2	CXC: DNA/RNA binding RING: MSL1 binding	Only male-specific subunit, targeting of the MSL complex to high-affinity sites (HAS)
MSL1	Coiled-coil: MSL2 binding PEHE: MOF binding	Scaffold protein, targeting of the MSL complex to HAS
MOF	Chromo-barrel: RNA binding ZnF: MSL1/histone binding MYST-HAT: H4K16 acetylation	Target gene activation and spreading of the MSL complex from HAS to active genes
MSL3	Chromo-barrel: RNA binding and H3K36me3 binding MRG: MSL1 binding	Stimulates and regulates specificity of MOF, facilitates spreading
MLE	DExH-family of helicases, two RNA-binding motifs	DNA/RNA helicase, integrates roX RNAs into MSL complex, facilitates RNA spreading, transcriptional activation
roX1/2	Long non-coding RNAs, functionally redundant, may form initial HAS, facilitate spreading	

Figure 2. The *Drosophila melanogaster* male dosage-compensation complex. The complex, called the MSL complex in *Drosophila*, consists of five proteins (MSL1, MSL2, MSL3, MOF, MLE) and two non-coding *roX* RNAs. The proteins, but not the *roX* RNAs, are evolutionarily conserved, as related proteins can be found in yeast and humans (for details see [30,68,69]). The box lists the conserved protein domains of the individual members of the *Drosophila* MSL complex and their identified functions for dosage compensation. MSL2 is the only male-specific protein subunit; all other subunits are present in both sexes. The two *roX* RNAs (see bottom of table) are also only expressed in males. The curved arrows symbolize the known enzymatic activities in the dosage-compensation complex. MLE is an RNA helicase that hydrolyzes ATP to effect conformational changes in DNA and RNA [70]. MOF is a lysine acetyltransferase with specificity for lysine 16 of histone H4. Abbreviations of the protein domains are: CXC, cysteine-rich domain; ZnF, zinc finger; PEHE, proline-glutamic acid-histidine-glutamic acid; HAT, histone acetyltransferase; MYST, MOZ (monocytic leukemia zinc finger protein), YBF2/SAS3 (something about silencing 3), SAS2 and TIP60 (60 kDa Tat-interactive protein); MRG, mortality factor on chromosome 4 related gene and DExH, aspartic acid-glutamic acid-x-histidine.

with graded activity states, which can be used either to completely switch off large chromosomal domains or to fine-tune transcription (either up or down) in the twofold range. Dosage compensation therefore integrates with other aspects of chromatin organization. In *Drosophila*, the male X chromosome that accumulates the H4K16 acetylation mark is particularly sensitive to mutations in general chromatin organizers. Prominent among these is the zinc finger protein Su(var)3-7 (suppressor of variegation 3-7), a heterochromatin constituent known to bind HP1 (heterochromatin protein 1). Normal levels of Su(var)3-7 are required for proper dosage compensation and to ensure the selective binding of the dosage-compensation complex to the X chromosome [41-43]. The male X polytene chromosome bloats when Su(var)3-7 levels are reduced and condenses when the protein is in excess. These changes in chromatin condensation depend on a functional dosage compensation complex, suggesting that the MOF-catalyzed acetylation of histone 4, and subsequent unfolding effect of H4K16ac, is constrained by as yet unknown counteracting factors (Figure 3a), conceivably by ones that promote chromatin compaction.

Selective, massive unfolding of the dosage-compensated male X chromosome in *Drosophila* is also observed when the nucleosome remodeling factor (NURF) is inactivated [44,45]. Nucleosome remodeling by NURF may thus also serve to counteract excessive unfolding due to H4K16 acetylation. Tamkun and colleagues [46] suggested that NURF might achieve this task by maintaining sufficiently high histone H1 levels on the X chromosome. Clearly, the degree of chromatin compaction can be adjusted by integration of unfolding and compacting factors.

Harnessing MOF for dosage compensation

Further analysis of the role of *Drosophila* MOF in dosage compensation suggests that it may affect gene expression by modulating the productivity of the transcription machinery in the chromatin context. Although MOF is able to acetylate non-histone substrates [47,48], its main substrate in the context of dosage compensation is the strategic H4K16. Biochemical studies showed that this modification interferes directly with the folding of the nucleosomal chain into 30-nm fibers *in vitro* [35,49]. Accordingly, H4K16 acetylation by MOF has the potential to counteract chromatin-mediated transcriptional repression [50,51] (Figure 3a). In the simplest scenario, the only task of the MSL complex in *Drosophila* would be to enrich MOF on the X chromosome relative to the autosomes. However, studies of the effect of MOF in yeast or in a cell-free chromatin transcription system showed that H4K16 acetylation does not automatically increase transcription by twofold, but by many-fold [50]. This strong activation potential of MOF can also be visualized in *Drosophila*. We recently established *Drosophila* lines in which MOF is tethered to a β-galactosidase reporter gene engineered to reside on an autosome [51]. Sorting adult flies according to sex allowed comparison of MOF-dependent reporter gene stimulation in male flies, where MOF is part of the dosage-compensation complex, and in females, where its molecular context was initially unknown. In females, MOF recruitment stimulated transcription from a proximal promoter by an order of magnitude. The effect faded with increasing distance between recruitment site and transcription start site and therefore appears to be related to local chromatin opening by promoter-bound co-activators.

By contrast, the molecular context of the MSL complex in males restricted the activation effect of MOF to the twofold range reminiscent of dosage compensation, and this effect was observable over a distance of 5 kb [51]. Notably, similar H4K16 acetylation levels accompanied the very different activation modes in the two sexes. So it seems that the activation potential of H4K16 acetylation revealed in females is constrained in males. Ectopic assembly of the MSL complex in females by expression of MSL2 constrained the strong activation to a twofold range [51]. We concluded from these and further studies that the *Drosophila* dosage-compensation complex achieves a twofold activation of transcription by integrating activating and repressive principles [51].

MOF serves as an example of the principle that dosage compensation employs chromatin modifiers that are also functional in other contexts. MOF is expressed at only slightly lower levels in females than in males, and it also resides in at least one other complex in addition to the MSL complex. Mendjan *et al*. [52] first reported the existence of an alternative complex (the NSL complex, for 'Non-Specific-Lethal') in mixed-sex embryos and male cells of *Drosophila*, which contained a number of poorly characterized nuclear proteins and two

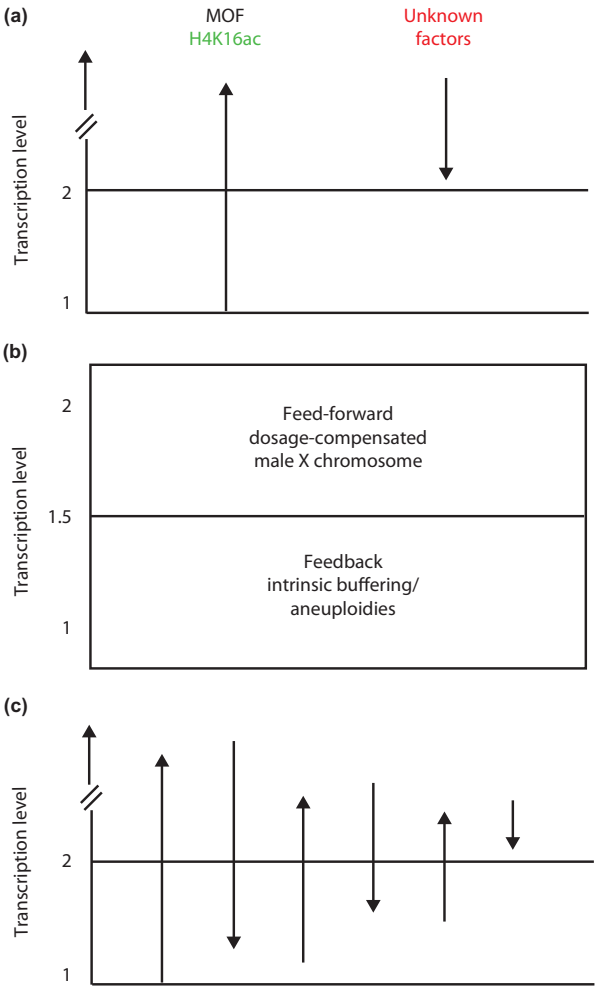


Figure 3. Possible mechanisms for dosage compensation. **(a)** The twofold activation of the single male X chromosome in *Drosophila* could be achieved by a large, MOF-dependent activation of transcription through H4K16 acetylation and its counteraction by yet unknown factors, mediated by the dosage-compensation complex in males [51]. In (a,b), transcriptional level 1 refers to the normal regulated level of transcription from a single uncompensated X chromosome in females. **(b)** Furthermore, the twofold activation of the male X chromosome could be achieved by a combination of mechanisms: a general buffering/feedback component and a dedicated feed-forward mechanism (dosage compensation as suggested in (a)) [7]. The effects of these two processes could add up to the expected twofold compensation required to equalize the expression of X-linked genes between the sexes. **(c)** Precise transcription levels could result from negotiation between a number of activating and repressive factors (up and down arrows). In this instance, transcriptional level 1 refers to a 'basal' transcription state. This hypothetical model assumes that additional factors beyond those mentioned in (a) and (b) contribute to final transcription levels, such as male-enriched protein kinases, heterochromatin components, chromatin remodelers, and others (for details, see text).

components of nuclear pores [52]. The closely related MOF-MBD-R2 complex, purified by us from female *Drosophila* cells [51], shares several prominent components with the NSL complex, including WDS (Will Die Slowly, a homolog of mammalian WDR5 (WD repeat-containing protein 5), dMCRS2 (microspherule protein 1), a forkhead-associated domain protein, and MBD-R2 (an uncharacterized protein harboring similarity to methyl-CpG-binding domains) [53]. In contrast to the NSL complex, the MOF-MBD-R2 complex does not contain nuclear pore components [51].

The evidence so far suggests that the MOF-MBD-R2 complex provides the molecular context for the strong activation elicited by MOF in females. Globally, MOF co-localizes with MBD-R2 to active genes with enrichment towards their 5' ends on all chromosomes in male and females, except for the male X chromosome (Figure 4). In male *Drosophila* cells, MOF is enriched on the X chromosome, where it co-localizes with MSL-complex components (such as MSL1) with a bias towards the 3' end (Figure 4). In male *Drosophila* cells, MOF apparently distributes dynamically between the two complexes. Ectopic expression of MSL2 in female cells, which leads to assembly of a dosage-compensation complex, re-localizes MOF from the autosomes to the X chromosome and from the 5' end to the 3' end of transcribed genes. The 3' enrichment suggests that dosage compensation in *Drosophila* may act at the level of transcription elongation [54,55].

The earlier notion that MOF, a global activator of transcription, was harnessed to balance the X-chromosomal monosomy in male *Drosophila* is supported by the fact that the H4K16-specific acetyltransferase activity has been conserved during evolution, although its biological function has not [56,57]. MOF (KAT8) is the best-studied member of the evolutionarily conserved family of MYST acetyltransferases (MOZ (monocytic leukemia zinc finger protein), YBF2/SAS3 (something about silencing 3), SAS2 and TIP60 (60 kDa Tat-interactive protein)). To the best of our knowledge, mammalian MOF is not involved in dosage compensation, but in regulating gene expression in more specific ways and in maintaining genome stability. Knock-down of human MOF impairs the signaling of DNA damage via the ATM pathway in response to double-strand breaks, causing increased cell death and a loss of the cell-cycle checkpoint response [58]. Mouse MOF is essential for oogenesis and embryogenesis [59]. Loss of H4K16ac is a cancer hallmark [60] and MOF is deregulated in a number of diseases [61,62].

As in *Drosophila*, mammalian MOF resides in several distinct complexes. These include the MOF-MLL1-NSL complex, which is required for the expression of the Hox 9a gene [63]; a complex containing the homologs of the *Drosophila* MSL3 and MSL1 that contributes to global H4K16 acetylation [64,65]; and a complex most closely related to the *Drosophila* NSL complex [52], containing human NSL1 (MSL1v1) and PHF20 (PHD finger protein 20, the homolog of MBD-R2), in addition to other NSL protein homologs. This complex has attracted particular attention as it is not only responsible for the majority of H4K16ac in human cells [66], but also acetylates p53 at lysine 120 (K120) [66,67]. p53 in which K120 is mutated can no longer trigger the apoptotic pathway, yet its role in the cell-cycle checkpoint is not impaired. Evidently, the substrate specificity of human MOF and the physiological processes in which it is involved are largely determined by the molecular context of the acetyltransferase, defined by the composition of the different complexes. In *Drosophila*, however, one of the complexes has been adapted to serve the goal of balancing the genome for dosage compensation.

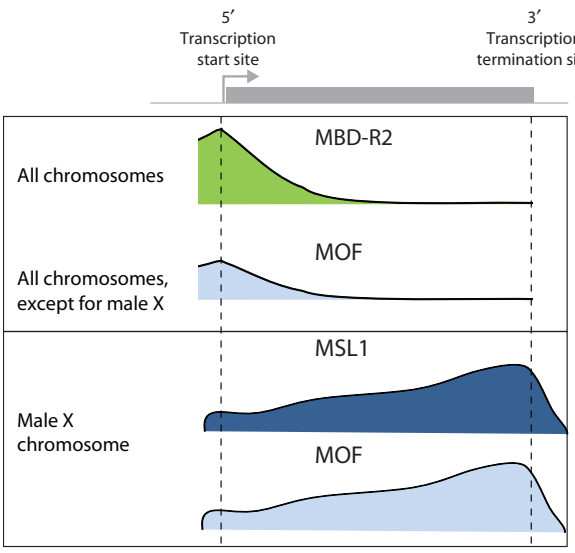


Figure 4. Schematic representation of the distribution of the key regulators of dosage compensation on a target gene in *Drosophila*. The gene is depicted as a gray bar at the top of the figure, with the arrow representing the transcription start site. The figure is based on genome-wide binding studies of MOF, MBD-R2 and MSL1. The upper panel shows that MBD-R2 is enriched at promoters (5') on all chromosomes in both sexes, underscoring its function as a general transcriptional facilitator. MOF co-localizes with the promoter peak of MBD-R2 on all chromosomes except for the male X chromosome, where it is more enriched towards the 3' end of the target gene as a result of its association with the dosage-compensation complex (bottom panel). The MSL1 profile serves as a marker for the presence of the dosage-compensation complex [51]. For details see text.

Negotiation for small effects

Although the mechanisms through which aneuploidies are compensated for are still mysterious, a number of overarching principles have emerged during recent years,

mainly through studies of the X-chromosome monosomies. First, there is no simple switch for 'two-fold up' or 'two-fold down'. Optimal expression levels are negotiated by opposing principles. The X-chromosomal expression in hermaphrodite *C. elegans* results from integration of a global, twofold increase in expression in both sexes and a different counteracting hermaphrodite-specific principle, which halves the expression again (Figure 1c).

The first genome-wide comparison of copy number and transcription in *Drosophila* revealed that a local or chromosomal hemizygosity is compensated for by the integration of at least two different mechanisms: an approximately 1.5-fold compensation can be attributed to general buffering or feedback effects, whereas the remaining compensation is contributed by the evolution of a feed-forward mechanism involving a dedicated dosage-compensation complex [7] (Figure 3b). Furthermore, the twofold activation in male *Drosophila* is a composite of a much larger stimulation, which is opposed by a repressive principle (Figure 3a). We therefore envisage that adjustment of the optimal gene expression levels may be a consequence of negotiation between a number of counteracting activating and repressing principles (Figure 3c). The complex and layered organization of chromatin appears to us as an advanced equalizer with many levers to allow optimal tuning of the transcription melody.

Acknowledgements

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