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REVIEW

Implications of the gene balance hypothesis for dosage compensation

James A. BIRCHLER (✉), Lin SUN, Ryan DONOHUE, Abhijit SANYAL, Weiwu XIE

Division of Biological Sciences University of Missouri, Columbia, MO 65211, USA

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Abstract **Dosage compensation refers to the equal expression between the sexes despite the fact that the dosage of the X chromosome is different in males and females. In *Drosophila* there is a twofold upregulation of the single male X. In triple X metafemales, there is also dosage compensation, which occurs by a two-thirds downregulation. There is a concomitant reduction in expression of many autosomal genes in metafemales. The male specific lethal (MSL) complex is present on the male X chromosome. Evidence is discussed showing that the MSL complex sequesters a histone acetyltransferase to the X chromosome to mute an otherwise increased expression by diminishing the histone acetylation on the autosomes. Several lines of evidence indicate that a constraining activity occurs from the MSL complex to prevent overcompensation on the X that might otherwise occur from the high level of acetylation present. Together, the evidence suggests that dosage compensation is a modification of a regulatory inverse dosage effect that is a reflection of intrinsic gene regulatory mechanisms and that the MSL complex has evolved in reaction in order to equalize the expression on both the X and autosomes of males and females.**

Keywords inverse dosage effect, male specific lethal complex, histone acetylation, metafemales

Introduction

The Gene Balance Hypothesis posits that genes encoding components of multisubunit complexes exhibit a dosage effect because the stoichiometric change in the quantities of subunits affects the kinetics and mode of assembly of the whole complex (e.g. Birchler and Newton, 1981; Birchler et al., 2001; Birchler et al., 2005; Birchler and Veitia, 2007; Veitia et al., 2008; Birchler and Veitia, 2010). This principle applies to any type of macromolecular complex but aspects of gene regulation have some of the most wide ranging implications. The process of gene regulation relies in general on multi-subunit complexes during signal transduction as well as the mechanism of transcription itself.

The types of dosage effects that are produced fall into two main categories (Birchler, 1979; Birchler and Newton, 1981; Devlin et al., 1988; Sabl and Birchler, 1993; Guo and Birchler, 1994; Birchler, 2010) (Fig. 1). In the first, there is a positive correlation of target gene expression with the dosage of the transcriptional regulator. In the second, more prevalent type, there is a negative or inverse correlation (Birchler, 1979; Birchler and Newton, 1981; Sabl and Birchler, 1993; Guo and Birchler, 1994; Birchler et al., 2001; Birchler et al., 2005; Birchler, 2010), with the regulator dosage. Target genes, when varied alone, tend to exhibit a gene dosage effect. Thus, when they are combined in a chromosomal dosage series with a regulator operating upon it that acts inversely, the two effects cancel each other to bring about dosage compensation in aneuploids (Birchler, 1979; 1981; 1992; Birchler et al., 1990; Birchler and Veitia, 2007) (Fig. 1). The proposition discussed in this article is that this effect has been capitalized upon for sex chromosome dosage compensation in *Drosophila*.

The effects found with aneuploidy can be reduced to the action of single genes. Using a leaky allele of the white eye color locus as a reporter, second site modifiers were sought that would increase or decrease the amount of pigment present. Over the course of two decades, 47 modifiers were found that could be assigned to different genes (Birchler et al., 2001). Clearly, these operate on other genes as well and likely operate in a hierarchy. Such a large number of modifiers of

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Correspondence: James A. BIRCHLER
E-mail: BirchlerJ@Missouri.edu

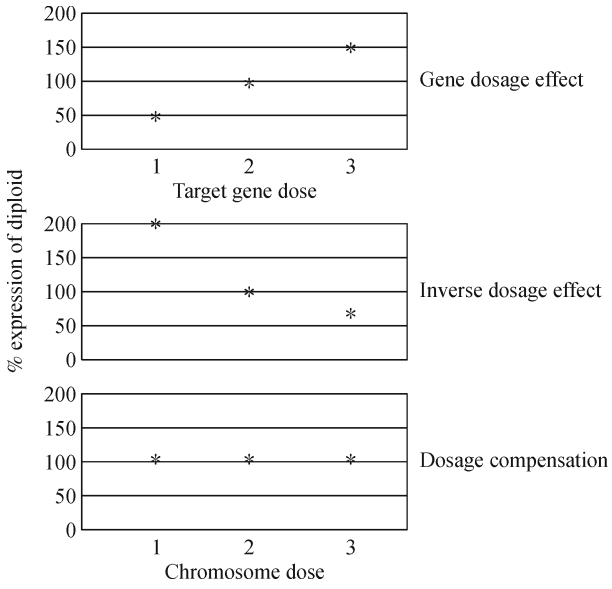

Figure 1 The relationship of gene dosage effects, the inverse regulatory effect and dosage compensation. The X axis reflects the relative amount of gene expression from a target gene. The Y axis reflects the gene or chromosomal dosage. Top: When a target gene is varied alone in dosage, its total expression is proportional to gene dosage. Middle: When the dosage of large chromosomal regions is varied in 1–3 doses, an inverse dosage effect operates on many target loci distributed in the genome. Bottom: When a target gene and a region that inversely affects it are varied at the same time, dosage compensation results. Thus, despite differential copy numbers of the chromosome, the total output is similar to the normal two dose diploid.

one phenotype were foreshadowed by the multigenic control of quantitative traits that exhibit additive (semi-dominant) effects (Guo and Birchler, 1994; Birchler et al., 2001; Birchler and Veitia, 2007; Veitia et al., 2008) and by the multigenic dosage sensitive modifiers of position effect variegation (Weiler and Wakimoto, 1995). Similar conclusions come from the finding of trans-acting dosage effects in human aneuploids (Bahn et al., 2002; Saran et al., 2003; Lyle et al., 2004; Aït Yahya-Graison et al., 2007; Altug-Teber et al., 2007) or aneuploid cancer cells (Phillips et al., 2001). Dosage effects of regulatory genes also have a role in many human diseases (Veitia and Birchler, 2010).

Dosage dependent regulatory genes and compensation

As noted above, the major type of trans-acting dosage effect is an inverse correlation of the target gene expression and the dosage of the regulator (Birchler et al., 2001). On the other hand, most target genes will exhibit a gene dosage effect when their copy number is varied (Grell, 1962). With the fact that many aneuploids will produce an inverse dosage effect (Devlin et al., 1988), the consequence is that dosage compensation occurs in many aneuploids (Devlin et al., 1982) with the basis being the cancellation of a structural gene dosage effect by the simultaneous inverse dosage effect operating on the same gene product (Birchler, 1981; Birchler et al., 1990). Previously, dosage compensation was found for the X chromosome of *Drosophila* (Muller, 1932; Arkhipova et al., 1997) and we propose that there is a relationship between the autosomal type of compensation and that which works for the X chromosome.

Dosage compensation

Dosage compensation refers to the equal expression from chromosomes at different copy numbers. Of particular note is the situation with sex chromosomes that have a dosage difference between the two sexes (Lucchesi et al., 2005). This phenomenon was first described in *Drosophila* by Herman Muller in 1932. The *white-apricot* allele of the *white* locus was varied in males and females and found to exhibit a gene dosage effect in each sex but each copy was doubled in expression in males relative to females. Thus, there is a twofold upregulation of most genes on the X chromosome in males.

The inverse dosage effect and X chromosome compensation

The twofold upregulation of the X chromosome implicates an inverse dosage effect as part of the process. Indeed, not only does compensation occur in males but it also operates in triple X metafemales (Margolis, 1934; Stern, 1960; Birchler et al., 1989; Birchler, 1992; Sun and Birchler, 2009). Thus, not only is there an inverse upregulation of the single X in males but there is an inverse two-thirds downregulation in metafemales to bring about compensation. To test directly for an inverse dosage effect of the X chromosome operating on the white eye color gene, a transgene present in a single copy on the autosomes was examined in flies that had the endogenous copy deleted on the X chromosome. The transgene in males is increased in expression relative to females and in turn reduced in expression in metafemales (Birchler, 1992). This finding illustrates that the dosage of the X chromosome produces an inverse dosage effect.

Recently, dosage compensation in metafemales was studied further by examining the expression of a number of X and autosomal genes (Sun and Birchler, 2009). All of the six X-linked genes (*v, Sgs4, y, G6pdh, r, 6Pgdh*) examined exhibited dosage compensation and six of the seven autosomal genes (*Adh, Tubulin, Ddc, Su(var)205, SevenUp, Rp49, Gpdh*) were reduced in expression relative to the segregating control females (Sun and Birchler, 2009). The individual gene expression was standardized to rRNA which in turn was shown not to vary in the two genotypes, thus establishing these changes as absolute “per cell” determinations rather than relative to each other. The autosomal

reductions reflect the typical "inverse dosage" effect of aneuploid states.

The concept that the dosage of the X chromosome produces an inverse dosage effect would predict that the autosomes in males would be increased in expression relative to females. We will discuss this concept in more detail below but we do note that for most transgenes that produce phenotypes that can be monitored quantitatively, there is usually a slightly greater autosomal expression in males than in females [e.g., *Adh*, *w-Adh*, *Adh-w* (Pal Bhadra et al., 1997; 1999; *brown* (Dreesen et al., 1991)]. Also, for leaky endogenous autosomal mutations, the most common sexual dimorphism is that the male expression is greater than the female (Smith and Lucchesi, 1969; Birchler, 1984).

Sequestration of the MSL complex to the X chromosome alters the genomic response to dosage dependent regulators

Another aspect of dosage compensation in *Drosophila* that must be accounted for involves the presence of the male specific lethal (MSL) complex that accumulates on the male X chromosome (Fig. 2). The consequence of this sequestration results from the fact that a member of the complex is a histone acetyltransferase that causes an increase in H4 lysine 16 acetylation (Kuroda et al., 1991; Turner et al., 1992; Bone et al., 1994; Hilfiker et al., 1997; Meller et al., 1997). Also, the JIL1 kinase is enriched on the male X and causes an increase in H3 phosphorylation (Jin et al., 1999; 2000; Wang et al., 2001). Mutations in the members of the complex are lethal to males but not females (Belote and Lucchesi, 1980). This fact and the accumulation of the MSL complex on the male X led to the idea that this complex and the histone modifications alone cause the twofold upregulation (Lucchesi et al., 2005). However, evidence presented below suggests that the MSL sequestration is a reaction to the genomic imbalance.

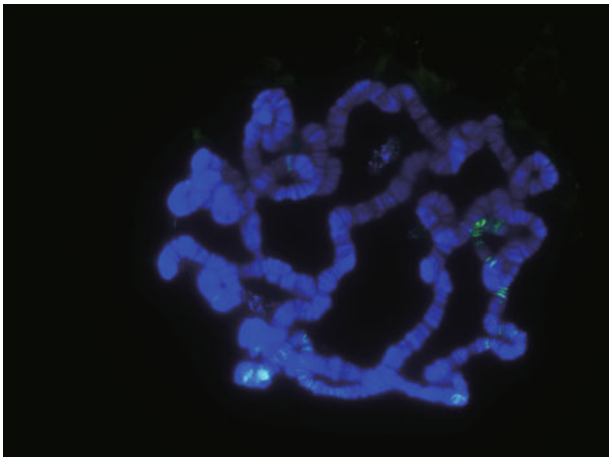

Figure 2 The MSL complex associates with the X chromosome in males. A polytene chromosome spread from a male is shown. Chromosomes are stained in blue with 4',6-diamidino-2-phenylindole (DAPI). The MSL2 protein is detected with immunolocalization and is in green.

Part of the argument that the MSL complex was responsible for dosage compensation comes from studies of gene expression in mutations in members of the complex. Originally, this was studied by examining autoradiographic grain counts over the X chromosome and portions of the autosomes in larval polytene chromosomes in mutant and normal genotypes (Belote and Lucchesi, 1980; Okuno et al., 1984). It is now known that the mutant causes a dissociation of the complex from the male X (Kuroda et al., 1991). The typical mode of normalization was to correct the X values by the autosomal values on the assumption that the autosomes did not change. However, this type of normalization will produce a change in ratio with either a change in expression of the X chromosome or a change in expression of the autosomes. The ratios did indeed show a lowered value (Belote and Lucchesi, 1980; Okuno et al., 1984) and were assumed to results from less X chromosome expression, i.e. a loss of dosage compensation. However, when the absolute values are examined, there is no change on the X but rather an autosomal increase (Hiebert and Birchler, 1994). Indeed, when many X and autosomal genes were assayed in the same genotype and normalized on a "per cell" basis, the overall effect was that most X-linked genes retained compensation in the *msl* mutants and many autosomal genes were increased (Hiebert and Birchler, 1994). This result suggested that the sequestration of the MSL complex was acting to mute the inverse effect on the autosomes that might be expected to otherwise occur.

The MSL complex is targeted to the X chromosome by the product of the *msl2* gene. The translation of this protein is blocked in females by the splicing factor *Sex lethal* (*Sxl*) (Kelley and Kuroda, 1995). All other members of the complex are present in both sexes (Bhadra et al., 1999). The histone acetylase that is part of the complex is encoded by the locus, *males absent on the first* (*mof*) (Hilfiker et al., 1997). It is capable of acetylating H4 on the male X and on all chromosomes in females (Bhadra et al., 1999). Thus, the level of acetylation is higher on the male X than the female Xs and the level on the autosomes is lower in males than in females (Bhadra et al., 1999). The *JIL1* gene product phosphorylates H3 and follows a similar mode of activity (Jin et al., 1999; 2000; Wang et al., 2001).

An explanation for the increased expression in the *msl* mutants is suggested by the fact that MOF gets redistributed in the mutant males to all chromosomes (Bhadra et al., 1999; Kind et al., 2008). The same is true of the distribution of MOF in mutations for the RNA components of the MSL complex (the roX RNAs) (Meller and Rattner, 2002). Thus, there is an increased amount of MOF on the autosomes of the mutants and a corresponding increase in H4 acetylation (Bhadra et al., 1999). Using *white* and *yellow* transgenes on the X and the autosomes, indeed there is no loss of compensation of these

transgenes in the *msl* mutants but there is an increased expression of the autosomal insertions (Bhadra et al., 1999) in concert with the effects observed on endogenous genes (Hiebert and Birchler, 1994).

One can test the reciprocal effect by ectopically causing the sequestration of the MSL complex in females. This can be performed by using a transgene of MSL2 that escapes the translational block of SXL. In this case, MSL2 is expressed and organizes the complex on the X chromosomes of females. When this occurs, the H4 acetylation that is usually uniform in females is concentrated on the X chromosomes because MOF to now localized there. When this circumstance is combined with transgenes of the *yellow* locus on the X or the autosomes, the X insertion is not increased and the autosomal version is reduced relative to normal females (Bhadra et al., 1999). We have extended this type of analysis to several X-linked and autosomal endogenous loci and have found the same result (Sun and Birchler, 2009). The MSL complex is also expressed in *Sxl* mutants in females and accumulates on the X chromosomes but has no impact on X gene expression (Bhadra et al., 2000).

Further evidence for a counter activity against histone acetylation has come from targeting experiments to a reporter (Prestel et al., 2010). The *mof* gene was fused with the GAL4 binding domain and targeted to *lacZ* and *mini-white* reporters. The targeting causes a strong accumulation of histone acetylation on the targets in both males and females. However, an impact on gene expression is only found in females. In males, in which the MSL complex is also brought to the reporter because of its association with MOF, a counter activity is present. This result provides further evidence that the MSL complex counteracts the high level of acetylation present on the male X.

A summary of these results can be stated that histone acetylation is correlated with increased expression except in the presence of the MSL complex, in which case it appears to be counteracted. In an experiment that targeted the fly MOF gene to a reporter in yeast, there was a dramatic increase in expression but this was 10-fold rather than twofold (Akhtar and Becker, 2000). It seems likely, therefore that the MSL complex has a constraining activity that prevents the over-expression of the male X, which might otherwise occur with the increased acetylation present there.

Dosage compensation in the absence of the MSL complex

As noted above, transgenes that are inserted into the autosomes show higher expression in males than in females, thus exhibiting partial dosage compensation (Roseman et al., 1995; Qian and Pirrotta, 1995), even in the absence of the MSL complex. This is consistent with the findings that loss of the MSL complex from the X also does not eliminate dosage compensation for the vast majority of X-linked genes (Hiebert and Birchler, 1994; Bhadra et al., 1999; 2000; Bhadra et al., 2005; Pal-Bhadra et al., 2006). Furthermore, in the Dipteran relative of flies, Sciara, there is no MSL2 gene and the MSL complex is present on all chromosomes in males (Ruiz et al., 2000) as occurs with *Drosophila* females. Clearly, it does not condition dosage compensation in this species. Lastly, the MSL complex is not assembled in the germline of flies (Rastelli and Kuroda, 1998) but there is nevertheless dosage compensation of X-linked genes that are expressed in the germline of both sexes (Parisi et al., 2003; Gupta et al., 2006).

Dosage compensation in *melanogaster-simulans* hybrids

Further evidence for the maintenance of dosage compensation in the absence of the MSL complex comes from the finding that hybrids between *Drosophila melanogaster* mothers and *D. simulans* fathers have a disruption of the sequestration of the MSL complex to the male X chromosome (Pal Bhadra et al., 2006). These males typically die before reaching the adult stage but survive to the late larval instar similarly to the mutants of components of the MSL complex. The basis of this disruption is that the *Sxl* lethal gene is aberrantly expressed in these males and thus prevents the translation of MSL2 (Pal Bhadra et al., 2006). A survey of gene expression of X and autosomal genes indicates that those on the X still have compensation and there is a generalized increase in expression of the autosomal genes (Pal Bhadra et al., 2006).

Interactions of chromatin components with the male X chromosome

Mutations in several chromatin components produce a bloated X chromosomal phenotype. These include the chromatin remodeling components *ISWI* (Deuring et al., 2000; Brehm et al., 2000), *nurf* (Badenhorst et al., 2002) as well as JIL-1 kinase (Wang et al., 2001) and the hetero-chromatin components, *HP1* and *Suvar3-7* (Delattre et al., 2004; Spierer et al., 2005). With regard to ISWI, the magnitude of this effect is dependent on the amount of H4 acetylation (Corona et al., 2002). It is possible that these gene products play a role in some way with the counter activity given that the mutant phenotype is enhanced by the level of acetylation. Indeed, in embryos that are mutant for ISWI, X-linked genes have an increased expression in males but not in females (Pal Bhadra et al., 2005), which would be consistent with a release of a counter activity against the acetylation level. Because the MSL complex is still present on the male X and still causing the sequestration of MOF, the high level of acetylation would now be capable of causing an increased expression.

A model for dosage compensation

There are five levels of gene expression that need to be explained by a valid model for dosage compensation (Birchler, 1996). Of course, the equal expression between males and females is the usual circumstance discussed with regard to compensation. However, as noted above, dosage compensation also occurs in metafemales (Stern, 1960; Lucchesi et al., 1974; Birchler et al., 1989; Birchler, 1992; Sun and Birchler, 2009). Compensation in metafemales is concomitant with autosomal reductions in expression (Birchler et al., 1989; Sun and Birchler, 2009).

In addition, dosage compensation has been documented in triploid genotypes. In the balanced triploid females with three sets of all chromosomes, the same per gene expression as diploid females is found (Maroni and Plaut, 1973; Lucchesi and Rawls, 1973a; Birchler et al., 1990). In comparison, when the X chromosome dosage is reduced to two copies in so-called triploid intersexes or even further to one copy in triploid metamales, compensation is still operative (Lucchesi and Rawls, 1973b; Lucchesi et al., 1977).

In all of these cases, the magnitude of change to accomplish dosage compensation is the inverse level of the X to autosomal imbalance. Gene expression in different ploidy levels has indeed been found to track the chromosomal imbalance (Rabinow et al., 1991; Guo and Birchler, 1994). This realization, together with the evidence noted above that an inverse effect has been directly observed with the dosage change of the X chromosome, further implicates an inverse dosage effect in the phenomenon of X chromosomal dosage compensation in *Drosophila*.

The presence of the MSL complex on the male X chromosome is therefore hypothesized to sequester chromatin modifiers from the autosomes in males to mute an inverse effect that would be expected to occur otherwise. However, this causes an accumulation of histone modifications on the male X chromosome and thus it is likely that the counter activity evolved to prevent an over-compensation. This concept can explain dosage compensation in all of the genotypes that exhibit it including those that have no MSL complex, such as metafemales. This concept can synthesize all of the data about gene expression in *msl* mutants, the lack of effect of ectopically expressed MSL2, the counter activity against acetylation by the MSL complex displayed in targeting experiments and the modulation of the magnitude of effect in different ploidy levels. Lastly, because the inverse effect is displayed by many aneuploids, an involvement in sex chromosome dosage compensation would be the natural progression from an intrinsic mechanism involved with eukaryotic gene expression.

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References

Aït Yahya-Graison E, Aubert J, Dauphinot L, Rivals I, Prieur M, Golfier G, Rossier J, Personnaz L, Creau N, Bléhaut H, Robin S, Delabar J M, Potier M C (2007). Classification of human chromosome 21 gene-expression variations in Down syndrome: impact on disease phenotypes. Am J Hum Genet, 81(3): 475–491

Akhtar A, Becker P B (2000). Activation of transcription through histone H4 acetylation by MOF, an acetyltransferase essential for dosage compensation in *Drosophila*. Mol Cell, 5(2): 367–375

Altug-Teber O, Bonin M, Walter M, Mau-Holzmann U A, Dufke A, Stappert H, Tekesin I, Heilbronner H, Nieselt K, Riess O (2007). Specific transcriptional changes in human fetuses with autosomal trisomies. Cytogenet Genome Res, 119(3–4): 171–184

Arkhipova I R, Li J, Meselson M (1997). On the mode of gene-dosage compensation in *Drosophila*. Genetics, 145(3): 729–736

Badenhorst P, Voas M, Rebay I, Wu C (2002). Biological functions of the ISWI chromatin remodeling complex NURF. Genes Dev, 16(24): 3186–3198

Bahn S, Mimmack M, Ryan M, Caldwell M A, Jauniaux E, Starkey M, Svendsen C N, Emson P (2002). Neuronal target genes of the neuron-restrictive silencer factor in neurospheres derived from fetuses with Down's syndrome: a gene expression study. Lancet, 359(9303): 310–315

Belote J M, Lucchesi J C (1980). Control of X chromosome transcription by the *maleless* gene in *Drosophila*. Nature, 285(5766): 573–575

Bhadra M P, Bhadra U, Kundu J, Birchler J A (2005). Gene expression analysis of the function of the male-specific lethal complex in *Drosophila*. Genetics, 169(4): 2061–2074

Bhadra U, Pal-Bhadra M, Birchler J A (1999). Role of the *male specific lethal* (*msl*) genes in modifying the effects of sex chromosomal dosage in *Drosophila*. Genetics, 152(1): 249–268

Bhadra U, Pal-Bhadra M, Birchler J A (2000). Histone acetylation and gene expression analysis of *sex lethal* mutants in *Drosophila*. Genetics, 155(2): 753–763

Birchler J A (1979). A study of enzyme activities in a dosage series of the long arm of chromosome one in maize. Genetics, 92(4): 1211–1229

Birchler J A (1981). The genetic basis of dosage compensation of *alcohol dehydrogenase-1* in maize. Genetics, 97(3–4): 625–637

Birchler J A (1984). Genetic analysis of a modifier of the sexual dimorphism of glass in *Drosophila melanogaster*. Genet Res, 44(02): 125–132

Birchler J A (1992). Expression of cis-regulatory mutations of the *white* locus in metafemales of *Drosophila melanogaster*. Genet Res, 59(1): 11–18

Birchler J A (1996). X chromosome dosage compensation in *Drosophila*. Science, 272(5265): 1190–1191

Birchler J A (2010). Reflections on studies of gene expression in aneuploids. Biochem J, 426(2): 119–123

Birchler J A, Bhadra U, Bhadra M P, Auger D L (2001). Dosage-dependent gene regulation in multicellular eukaryotes: implications for dosage compensation, aneuploid syndromes, and quantitative traits. Dev Biol, 234(2): 275–288

Birchler J A, Hiebert J C, Krietzman M (1989). Gene expression in adult metafemales of *Drosophila melanogaster*. Genetics, 122(4): 869–879

Birchler J A, Hiebert J C, Paigen K (1990). Analysis of autosomal

dosage compensation involving the *alcohol dehydrogenase* locus in *Drosophila melanogaster*. Genetics, 124(3): 679–686

Birchler J A, Newton K J (1981). Modulation of protein levels in chromosomal dosage series of maize: the biochemical basis of aneuploid syndromes. Genetics, 99(2): 247–266

Birchler J A, Riddle N C, Auger D L, Veitia R A (2005). Dosage balance in gene regulation: biological implications. Trends Genet, 21(4): 219–226

Birchler J A, Veitia R A (2007). The gene balance hypothesis: from classical genetics to modern genomics. Plant Cell, 19(2): 395–402

Birchler J A, Veitia R A (2010). The gene balance hypothesis: implications for gene regulation, quantitative traits and evolution. New Phytol, 186(1): 54–62

Bone J R, Lavender J, Richman R, Palmer M J, Turner B M, Kuroda M I (1994). Acetylated histone H4 on the male X chromosome is associated with dosage compensation in *Drosophila*. Genes Dev, 8 (1): 96–104

Brehm A, Längst G, Kehle J, Clapier C R, Imhof A, Eberharter A, Müller J, Becker P B (2000). dMi-2 and ISWI chromatin remodelling factors have distinct nucleosome binding and mobilization properties. EMBO J, 19(16): 4332–4341

Corona D F, Clapier C R, Becker P B, Tamkun J W (2002). Modulation of ISWI function by site-specific histone acetylation. EMBO Rep, 3 (3): 242–247

Delattre M, Spierer A, Jaquet Y, Spierer P (2004). Increased expression of *Drosophila Su(var)3-7* triggers *Su(var)3-9*-dependent heterochromatin formation. J Cell Sci, 117(Pt 25): 6239–6247

Deuring R, Fanti L, Armstrong J A, Sarte M, Papoulas O, Prestel M, Daubresse G, Verardo M, Moseley S L, Berloco M, Tsukiyama T, Wu C, Pimpinelli S, Tamkun J W (2000). The ISWI chromatin-remodeling protein is required for gene expression and the maintenance of higher order chromatin structure in vivo. Mol Cell, 5(2): 355–365

Devlin R H, Holm D G, Grigliatti T A (1982). Autosomal dosage compensation *Drosophila* melanogaster strains trisomic for the left arm of chromosome 2. Proc Natl Acad Sci U S A, 79(4): 1200–1204

Devlin R H, Holm D G, Grigliatti T A (1988). The influence of whole-arm trisomy on gene expression in *Drosophila*. Genetics, 118(1): 87–101

Dreesen T D, Henikoff S, Loughney K (1991). A pairing-sensitive element that mediates trans-inactivation is associated with the *Drosophila* brown gene. Genes Dev, 5(3): 331–340

Gergen J P (1987). Dosage compensation in *Drosophila*: Evidence that *daughterless* and *Sex-lethal* control X chromosome activity at the blastoderm stage of embryogenesis. Genetics, 117(3): 477–485

Grell E H (1962). The dose effect of ma-l^{+} and ry^{+} on xanthine dehydrogenase activity in *Drosophila melanogaster*. Z Vererbungsl, 93(3): 371–377

Guo M, Birchler J A (1994). Trans-acting dosage effects on the expression of model gene systems in maize aneuploids. Science, 266 (5193): 1999–2002

Gupta V, Parisi M, Sturgill D, Nuttall R, Doctolero M, Dudko O K, Malley J D, Eastman P S, Oliver B (2006). Global analysis of X-chromosome dosage compensation. J Biol, 5(1): 3

Hiebert J C, Birchler J A (1994). Effects of the *maleless* mutation on X and autosomal gene expression in *Drosophila melanogaster*. Genetics, 136(3): 913–926

Hilfiker A, Hilfiker-Kleiner D, Pannuti A, Lucchesi J C (1997). mof, a putative acetyl transferase gene related to the Tip60 and MOZ human genes and to the SAS genes of yeast, is required for dosage compensation in *Drosophila*. EMBO J, 16(8): 2054–2060

Jin Y, Wang Y, Johansen J, Johansen K M (2000). JIL-1, a chromosomal kinase implicated in regulation of chromatin structure, associates with the male specific lethal (MSL) dosage compensation complex. J Cell Biol, 149(5): 1005–1010

Jin Y, Wang Y, Walker D L, Dong H, Conley C, Johansen J, Johansen K M (1999). JIL-1: a novel chromosomal tandem kinase implicated in transcriptional regulation in *Drosophila*. Mol Cell, 4(1): 129–135

Kelley R L, Kuroda M I (1995). Equality for X chromosomes. Science, 270(5242): 1607–1610

Kind J, Vaquerizas J M, Gebhardt P, Gentzel M, Luscombe N M, Bertone P, Akhtar A (2008). Genome-wide analysis reveals MOF as a key regulator of dosage compensation and gene expression in *Drosophila*. Cell, 133(5): 813–828

Kuroda M I, Kernan M J, Kreber R, Ganetzky B, Baker B S (1991). The *maleless* protein associates with the *X* chromosome to regulate dosage compensation in *Drosophila*. Cell, 66(5): 935–947

Lucchesi J C, Belote J M, Maroni G (1977). X-linked gene activity in metamales (XY;3A) of *Drosophila*. Chromosoma, 65(1): 1–7

Lucchesi J C, Kelly W G, Panning B (2005). Chromatin remodeling in dosage compensation. Annu Rev Genet, 39(1): 615–651

Lucchesi J C, Rawls J M Jr (1973a). Regulation of gene function: a comparison of enzyme activity levels in relation to gene dosage in diploids and triploids of *Drosophila melanogaster*. Biochem Genet, 9 (1): 41–51

Lucchesi J C, Rawls J M Jr, Maroni G (1974). Gene dosage compensation in metafemales (3X;2A) of *Drosophila*. Nature, 248 (449): 564–567

Lucchesi J C, Rawls R M Jr (1973b). Regulation of gene function: a comparison of X-linked enzyme activity levels in normal and intersexual triploids of *Drosophila melanogaster*. Genetics, 73(3): 459–464

Lyle R, Gehrig C, Neergaard-Henrichsen C, Deutsch S, Antonarakis S E (2004). Gene expression from the aneuploid chromosome in a trisomy mouse model of down syndrome. Genome Res, 14(7): 1268–1274

Margolis O S (1934). The effect of a supernumerary X chromosome on members of the Bar series of *Drosophila*. Genetics, 19(1): 18–24

Maroni G, Plaut W (1973). Dosage compensation in *Drosophila melanogaster* triploids. I. Autoradiographic study. Chromosoma, 40 (4): 361–377

Meller V H, Rattner B P (2002). The roX genes encode redundant male-specific lethal transcripts required for targeting of the MSL complex. EMBO J, 21(5): 1084–1091

Meller V H, Wu K H, Roman G, Kuroda M I, Davis R L (1997). *roX1* RNA paints the X chromosome of male *Drosophila* and is regulated by the dosage compensation system. Cell, 88(4): 445–457

Muller H J (1932). Further studies on the nature and causes of gene mutations. Proc 6th Int Congr Genetics, 1: 213–255

Okuno T, Satou T, Oishi K (1984). Studies on the sex-specific lethals of *Drosophila melanogaster*. VII. Sex-specific lethals that do not affect dosage compensation. Jpn J Genet, 59(3): 237–247

Pal-Bhadra M, Bhadra U, Birchler J A (1997). Cosuppression in *Drosophila*: gene silencing of *Alcohol dehydrogenase* by *white-Adh*

transgenes is Polycomb dependent. Cell, 90(3): 479–490

Pal-Bhadra M, Bhadra U, Birchler J A (1999). Cosuppression of nonhomologous transgenes in *Drosophila* involves mutually related endogenous sequences. Cell, 99(1): 35–46

Pal Bhadra M, Bhadra U, Birchler J A (2006). Misregulation of *Sex-lethal* and disruption of MSL localization in *Drosophila* species hybrids. Genetics, 174: 1151–1159

Parisi M, Nuttall R, Naiman D, Bouffard G, Malley J, Andrews J, Eastman S, Oliver B (2003). Paucity of genes on the *Drosophila* X chromosome showing male-biased expression. Science, 299(5607): 697–700

Phillips J L, Hayward S W, Wang Y, Vasselli J, Pavlovich C, Padilla-Nash H, Pezullo J R, Ghadimi B M, Grossfeld G D, Rivera A, Linehan W M, Cunha G R, Ried T (2001). The consequences of chromosomal aneuploidy on gene expression profiles in a cell line model for prostate carcinogenesis. Cancer Res, 61(22): 8143–8149

Prestel M, Feller C, Straub T, Mitlöhner H, Becker P B (2010). The activation potential of MOF is constrained for dosage compensation. Mol Cell, 38(6): 815–826

Qian S, Pirrotta V (1995). Dosage compensation of the *Drosophila white* gene requires both the X chromosome environment and multiple intragenic elements. Genetics, 139(2): 733–744

Rabinow L, Nguyen-Huynh A T, Birchler J A (1991). A trans-acting regulatory gene that inversely affects the expression of the white, brown and scarlet loci in *Drosophila*. Genetics, 129(2): 463–480

Rastelli L, Kuroda M I (1998). An analysis of *maleless* and histone H4 acetylation in *Drosophila melanogaster* spermatogenesis. Mech Dev, 71(1–2): 107–117

Roseman R R, Swan J M, Geyer P K (1995). A *Drosophila* insulator protein facilitates dosage compensation of the X chromosome min-white gene located at autosomal insertion sites. Development, 121 (11): 3573–3582

Ruiz M F, Esteban M R, Doñoro C, Goday C, Sánchez L (2000). Evolution of dosage compensation in Diptera: the gene *maleless* implements dosage compensation in *Drosophila* (Brachycera sub-order) but its homolog in Sciara (Nematocera suborder) appears to play no role in dosage compensation. Genetics, 156(4): 1853–1865

Sabl J F, Birchler J A (1993). Dosage dependent modifiers of white alleles in *Drosophila melanogaster*. Genet Res, 62(1): 15–22

Saran N G, Pletcher M T, Natale J E, Cheng Y, Reeves R H (2003). Global disruption of the cerebellar transcriptome in a Down syndrome mouse model. Hum Mol Genet, 12(16): 2013–2019

Smith P D, Lucchesi J C (1969). The role of sexuality in dosage compensation in *Drosophila*. Genetics, 61(3): 607–618

Spierer A, Seum C, Delattre M, Spierer P (2005). Loss of the modifiers of variegation Su(var)3-7 or HP1 impacts male X polytene chromosome morphology and dosage compensation. J Cell Sci, 118(Pt 21): 5047–5057

Stern C (1960). Dosage compensation–development of a concept and new facts. Can J Genet Cytol, 2: 105–118

Sun X, Birchler J A (2009). Interaction study of the male specific lethal (MSL) complex and trans-acting dosage effects in metafemales of *Drosophila melanogaster*. Cytogenet Genome Res, 124(3–4): 298–311

Turner B M, Birley A J, Lavender J (1992). Histone H4 isoforms acetylated at specific lysine residues define individual chromosomes and chromatin domains in *Drosophila* polytene nuclei. Cell, 69(2): 375–384

Veitia R A, Birchler J A (2010). Dominance and gene dosage balance in human health and disease. J Pathol, 220: 174–185

Veitia R A, Bottani S, Birchler J A (2008). Cellular reactions to gene dosage imbalance: genomic, transcriptomic and proteomic effects. Trends Genet, 24(8): 390–397

Wang Y, Zhang W, Jin Y, Johansen J, Johansen K M (2001). The JIL-1 tandem kinase mediates histone H3 phosphorylation and is required for maintenance of chromatin structure in *Drosophila*. Cell, 105(4): 433–443

Weiler K S, Wakimoto B T (1995). Heterochromatin and gene expression in *Drosophila*. Annu Rev Genet, 29(1): 577–605