REVIEW ARTICLE

A brief history of dosage compensation

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Abstract

In 1914, H. J. Muller postulated the origin of the Y chromosome as having resulted from restricted recombination between homologous sex chromosomes in the male and the accumulation of deleterious mutations. This evolutionary process leads to dosage compensation. This article lays out a brief history of dosage compensation in genetics.

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A hundred years ago, H. J. Muller, while a graduate student in the T. H. Morgan laboratory at Columbia University, New York, USA, postulated correctly the origin of the Y chromosome as a derived chromosome resulting from restricted recombination between original homologous sex chromosomes in the male and the accumulation of deleterious mutations (1914). Muller's explanation has been modified and expanded (Charlesworth 1978) and this process of whittling away of the incipient Y is now called Muller's ratchet (Felsenstein 1974). It is this evolutionary process that leads to dosage compensation.

Early *Drosophila* workers realized that the phenotypes for most X-linked genes were similar, if not identical, in the two sexes (Bridges 1922; Goldschmidt 1927; Mohr 1923). Goldschmidt (1954) ascribed these similarities and differences in 1X males and 2X females to differences in sexual development. Stern (1929) considered the possibility that evolutionary pressure could have brought about genetic changes that led to this pattern. It remained for Muller (1932) to present a concise explanation of the similarity of phenotypes for X-linked genes in *Drosophila* males and females. Working with X-linked hypomorphic eye colour mutations, Muller (1932) showed that females with one mutant copy and one deletion had a more severe phenotype than males with a single mutant gene. Males with a duplication of the mutation on a single X had a phenotype more like normal than did females with a mutant gene on each X (Muller 1932). Muller thought that these observations and others were compatible with hyperexpression of the male X, a mechanism he envisioned to be responsible for the equality of expression of X-linked genes in male and female *Drosophila*. He coined the expression 'dosage compensation' to describe this phenomenon.

By observing the results of adding X chromosome fragments containing the eye colour gene to males and females, Muller demonstrated that resulting phenotypic changes were due to dosage differences and not to a difference in the action of the gene in males and females. In addition, Muller (1932) showed that other genes on the X chromosome, later called compensators, were major factors in bringing about dosage compensation. His explanation of dosage compensation in *Drosophila* in general outline is remarkable in its precocity.

Cytological studies of *Drosophila* salivary gland chromosomes by Offerman (1936), a former colleague of Muller, showed that the cross-sectional area of the male X is as great as the paired Xs of the female. Although Offerman did not suggest any relationship of this observation to dosage compensation, this may be the first cytological evidence for hyperactivity of the male X in *Drosophila.* Remarkably, following Muller's (1932) presentation, no report on dosage compensation in any organism appeared until Muller's (1950a) Harvey lecture, 'evidence of the precision of genetic adaptation'. In his Harvey lecture, Muller presented a greatly expanded version of his 1932 presentation. In 1950, his emphasis was on evolutionary forces that brought about dosage compensation. Muller then considered the possibility that dosage compensation could have evolved through depression of X-linked gene activity in the female, as well as by hyperexpression of the male X. He appeared to favour his new idea of depression of X-linked activity in the female (Muller 1950a).

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Within a few years of publishing the Harvey lecture, two relevant cytological studies were reported: (i) a study by Aronson *et al.* (1954) that confirmed Offerman's (1936) finding that the male salivary gland X has the same cross-sectional area as the paired females Xs and added the finding that the single male X had half the DNA content of the two female Xs, establishing that the enlargement of the male X was not a result of extra replication; and (ii) a study by Dobzhansky (1957) of a *Drosophila* species hybrid in which the homologous X chromosomes in salivary glands were not paired, thus eliminating any possible effect of pairing on the observations. Again, the cross-sectional area of the male X was found to be equal to the combined areas of the two female Xs. In light of the Aronson *et al.* (1954) DNA measurements, Dobzhansky (1957) concluded that the enlarged male X cross-sectional area was due to increased expression activity to achieve dosage compensation.

Following Dobzhansky's (1957) report, 7 years passed before another research paper on dosage compensation in *Drosophila* appeared, and it was by a group of human geneticists (Young *et al.* 1964). This long hiatus is reflected in Stern's (1960) comment that there was little interest in dosage compensation. Supporting this notion is the fact that Muller's (1950a) Harvey lecture, a paper devoted entirely to the concept of dosage compensation and which must be considered a major contribution, has been cited only 19 times in over 60 years. By contrast, in the same year as the Harvey lecture, Muller gave a presidential address to the American Society of Human Genetics, entitled 'Our load of mutations' that has been cited nearly 500 times (Muller 1950b). Prior to the Harvey lecture, Muller had presented important ideas relative to dosage compensation in two papers (Muller 1914, 1932), but the main topics of those papers were unrelated to dosage compensation and their citation numbers would therefore not be relevant.

Also supportive of the lack of interest in dosage compensation at the time is the fact that the 1950 edition of the widely adopted genetics textbook by Sinnott, Dunn and Dobzhansky makes no mention of the subject, as was the case 12 years later in Sturtevant and Beadle's '*Introduction to genetics*'. The latter omission is most surprising, since Muller (1914) acknowledges Sturtevant's collaboration in his paper in developing the model for the origin of the Y chromosome, responsible for dosage compensation.

I was a postdoctoral fellow at the Institute for the Study of Human Variation at Columbia University from 1952 to 1957, where L. C. Dunn and Theodosius Dobzhansky were senior faculty members. I do not recall dosage compensation ever being mentioned by faculty members or by any of the notable scientists who visited during that period. As mentioned earlier, Dobzhansky (1957) published a paper reporting cytological evidence for enhanced expression of the X in the male as the basis of dosage compensation in *Drosophila.* I do not recall this work ever being discussed or talked about at Columbia. I do recall a talk by the popular physical anthropologist, Ashley Montague, a good friend of Dobzhansky, in which he expressed his view that the superiority of women is due to their having two X chromosomes compared to the male's single X. The possibility of nature's affirmative action via an equalizing effect of dosage compensation was not mentioned by Montague or any member of the audience.

Meanwhile, the story on dosage compensation in mammals was in the beginning stages. Barr and Bertram (1949) described a heterochromatic structure in female mammalian nuclei, now known as the Barr body, that they interpreted (incorrectly, as we now know) as being due to association of the heterochromatic portions of the two X chromosomes. Recognition of the Barr body as a single heteropycnotic (inactive) X chromosome came only a decade later (Ohno *et al.* 1959). Had Barr and Bertram made the correct interpretation, our understanding of mammalian dosage compensation might have been advanced by a decade. In the same year, Welshons and Russell (1959) reported that a single X is sufficient for XO female mouse to be viable and fertile, which could also have led to the notion of a single active X in females as the basis of mammalian dosage compensation. Remarkably, Curt Stern, one of the early students of *Drosophila* dosage compensation and the author of an early and significant human genetics text book, reviewed all these observations without making any connection to dosage compensation in mammals (Stern 1960).

About this time, two mouse geneticists working independently, Mary Lyon and Liane Russell, made similar observations: that variegation in coat character expression is associated with certain X-linked genes and with certain autosomal genes translocated to the X chromosome. In 1961, Lyon correctly interpreted the X-linked variegation as being due to random and permanent somatic inactivation of either the paternal or maternal X chromosome in individual cells of the female early in development (Lyon 1961). However, dosage compensation was not mentioned. In that same year, Russel (1961) explained the murine X-linked-associated variegation as requiring the presence of two X chromosomes, one of which she thought could bring about variegation. Again, dosage compensation was not mentioned. Although the Russell's explanation was certainly not as clear as Lyon's, it was similar.

In the same period, two groups of human geneticists were interested in X chromosome behaviour. Morishima *et al.* (1962) focussed on differential replication time in the cell cycles of the two female X chromosomes. They showed that two populations of cells exist with respect to time of replication and made a brief reference to implications for dosage compensation. Beutler *et al.* (1962), working with heterozygotes for the X-linked gene glucose-6-phosphate dehydrogenase, showed the existence of two populations of red blood cells and discussed briefly the implications of their findings for dosage compensation in mammals. Lyon (1962), in her second paper on X inactivation, notes only in the summary that X inactivation explains dosage compensation in mammals.

Thus, by 1962, it was becoming clear that dosage compensation in mammals involved X chromosome inactivation in the female, or in Muller's terms, depression of X-linked activity in the female. The rapid acceptance of X inactivation as the underlying mechanism of mammalian dosage compensation was probably due to the accompanying easily visible Barr body or heteropycnotic X chromosome, an accepted marker of genetic inactivity.

In 1962, however, the equivalent explanation of dosage compensation in *Drosophila* was far from resolved, some 30 years after Muller introduced the concept (Muller and Kaplan 1966). Cytological studies in *Drosophila* of Offerman (1936), Aronson *et al.* (1954) and Dobzhansky (1957), all favoured the idea of enhanced activity of the male X as the underlying mechanism of dosage compensation in *Drosophila*. In fact, Dobzhansky (1957) was quite positive about this point. Muller and Kaplan (1966), however, appeared to be antagonistic to these salivary gland measurement studies. I suspect that his antipathy to these results was because they supported hyperactivity of the male X as the primary mechanism of dosage compensation, a view that he did not favour. In fact, in his last papers (Muller and Kaplan 1964, 1966), he criticizes the cytological studies on the basis of improper interpretation of salivary gland volume measurements. Apparently, Muller was not aware of the Mukherjee and Beermann (1965) paper demonstrating equivalent transcriptional activities in *Drosophila* male and female salivary gland X chromosomes, as well as similar X:autosome ratios of transcription in the two sexes. The results of this study might have made it more difficult for him to maintain his opposition to hyperactivity of the male X as the basis of dosage compensation in *Drosophila.*

Muller's last papers (Muller and Kaplan 1964, 1966) were the result of work done during 1964–65 as a member of the Institute for Advanced Learning at the City of Hope Medical Centre, where his coauthor, W. D. Kaplan was a regular member. Kaplan was a *Drosophila* geneticist who did postdoctoral work with Mary Lyon on radiation genetics several years before her interest changed to X-linked variegation. Kaplan moved to the City of Hope Medical Centre where he collaborated with S. Ohno on the critical work demonstrating that the Barr body was a single heterochromatic X chromosome (Ohno *et al.* 1959). E. Beutler was also at the City of Hope at that time and studied X-linked glucose-6-phosphate dehydrogenase variation in human red blood cells. He had independently demonstrated human X chromosome inactivation (as noted earlier) and discussed its implications for human dosage compensation. Bruce Cattanach (Ohno and Cattanach 1962), whose work led to the identification of the X inactivation centre (Cattanach and Issacson 1967) had worked earlier at the City of Hope with S. Ohno. It is also likely that Ohno would have been working on his well-known book 'Sex chromosomes and sex-linked genes' (1967) at this time. A significant portion of the book is devoted to the subject of dosage compensation. Thus, the general atmosphere at the City of Hope during this period must have been teeming with ideas of dosage compensation and may have influenced some of Muller's arguments as well as Ohno's ideas.

In his last paper, Muller and Kaplan (1966) considers the possibility that reduced female X chromosome expression occurs in both *Drosophila* and mammals and is the primary mechanism of dosage compensation. He sees, however, a distinct difference between the mammalian and *Drosophila* systems: he refers to the mammalian system as having evolved in a 'wholesale' fashion and the *Drosophila* system as having evolved 'piecemeal' or in Darwinian fashion. It must be more than a coincidence that these same ideas are presented in Susumu Ohno's (1967) book, 'Sex chromosomes and sex-linked genes'. Ohno uses the same term as Muller, 'piecemeal', to describe the evolution of dosage compensation in *Drosophila*, and instead of 'wholesale' for mammals, he writes 'It is likely that dosage compensation was accomplished for all the X-linked genes in one sweep by heterochromatinization of one of the two Xs of the female (Ohno 1967). Neither, Muller nor Ohno refers to the other in the context of these ideas. Ohno differed from Muller with regard to dosage compensation in one important respect in that he considered dosage compensation in *Drosophila* to be controlled primarily by enhanced expression of the male X (Ohno 1967). Ohno (1967) does not give any justification for this view, although he must have been aware of the cytological evidence, including the recent Mukherjee and Beermann (1965) paper. From Ohno's remarks about the evolution of mammalian dosage compensation (Ohno 1967), which he realized was complicated, I suspect that he favoured enhancement of expression of the male X in *Drosophila* because it was so simple. Doubling of expression of the single male X equalizes female and male X chromosome expression and recreates the quantitative relationships between the Xs and autosomes in males and females that existed prior to dosage compensation. Inactivation of one female X chromosome can bring about equality of male : female X chromosome expression, but then both male and female active Xs have to be doubled in expression to recreate the predosage compensation conditions. A number of recent papers have discussed this aspect of dosage compensation (Lin *et al.* 2007; Xiong *et al.* 2010; Deng *et al.* 2011).

I am still surprised that deep thinkers such as Muller and Ohno could feel that mammalian dosage compensation could come about in macro evolutionary steps. Of course, we now know that the random X inactivation system of placental mammals likely evolved from the nonrandom paternal X inactivation dosage compensation system characteristic of marsupials (Brown and Chandra 1973) and that the *XIST* gene evolved from a marsupial protein coding gene (Duret *et al.* 2006). It seems likely that both the *Drosophila* and mammalian dosage compensation systems evolved in a 'piecemeal' or Darwinian fashion, with the remarkable difference that one led to enhancement and the other to suppression of X-linked gene expression.

In the early 1960s no one was aware of the large number of autosomal mammalian genes that are expressed monoallelically. Awareness of that might have stimulated consideration of the possibility that such phenomenon could form the basis for the evolutionary initiation of mammalian X inactivation silencing. About the same time, however, it became clear that autosomal immunoglobulin genes did exhibit monoallelic expression. Some 20 years later, imprinted mammalian autosomal genes were found to exhibit monoallelic expression (Cattanach and Kirk 1985), and several years after that Buck and Axel (1991) showed that autosomal odorant receptor genes also did. More recently, it has been shown that monoallelic expression is very widespread (Gimelbrant *et al.* 2007). On the other hand, there is no evidence for widespread monoallelic expression in *Drosophila*.

Muller was impressed with the difference between the *Drosophila* and mammalian forms of dosage compensation, even when he thought that both systems involved depression of X expression in the female. Of course, the underlying mechanism of mammalian dosage compensation is almost the exact opposite of the one used by *Drosophila*. As it turns out, these two evolutionary solutions to the same problem may represent just the extremes that different species have taken for the control of sex chromosome dosage differences. Shortly after Mary Lyon's work, Ohno and colleagues showed that the creeping vole had a single X in the somatic cells of both sexes as a mechanism of dosage compensation (Ohno 1967). Studies on dosage compensation in nematodes did not begin until the 1980s (Wood *et al.* 1985), and the mechanism turns out to be different from both mammals and *Drosophila* : gene expression of both Xs in the female is depressed (Meyer 2010). Even before these latter observations were made, Muller felt that the variability in forms of dosage compensation indicated the evolutionary importance of the process, but in addition, he pointed out that in evolution anything is accepted that works sufficiently well.

I am struck by how little influence Muller, a giant of genetic thought and the originator of the important concepts of dosage compensation, seems to have had on the development of this subject, especially in *Drosophila*. His major work on dosage compensation, the Harvey lecture of 1950, has been cited a mere 19 times; in contrast, Mary Lyon's (1961) one page paper on X inactivation, which explains but does not mention either mammalian dosage compensation or Muller's work on *Drosophila*, has been cited over 2000 times. X inactivation as the underlying mechanism of mammalian dosage compensation was universally accepted within a few years of Mary Lyon's paper. It was at least another 20 years before there was wide acceptance of upregulation of the male X as the underlying mechanism of dosage compensation in *Drosophila* (Baker *et al.* 1994).

Today, almost a century after Muller's (1914) seminal paper, studies of dosage compensation in *Drosophila* abound: in the 50 years following Muller's (1914) paper, there were probably not more than 10 papers on dosage compensation in *Drosophila*. In the 50 years following Lyon's (1961) X inactivation paper, there were over 500 papers on *Drosophila* dosage compensation. In the last year alone, there were probably close to 50 papers on that subject.

It may be that turning off an X is more readily accepted than enhancing its expression. It is also possible that *Drosophila* geneticists are more difficult to persuade than their mammalian counterparts. I think it was the prestige and dominance of Muller that muffled critics of his views. Even a researcher as eminent as Dobzhansky only published once on the subject of *Drosophila* dosage compensation (1957). Mukherjee and Beermann (1965) were very careful in interpreting their work in which they show similar transcriptional activities in the single male and paired female Xs of *Drosophila*: 'From our results, however, we cannot draw any definite conclusions as to whether dosage compensation is a phenomenon involving repression or activation, i.e., works in the female or male. A few years later in an extension of the 1965 work, Lakhotia and Mukherjee (1969) argued that dosage compensation in *Drosophila* was due to hyperactivity of the single X chromosome in the male. In contrast, in 1973, in what may be the first review of dosage compensation in *Drosophila*, Lucchesi (1973) concluded that it was not possible to distinguish between the models of hyperactivity of the male X versus decreased activity of the Xs in the female as the basis of *Drosophila* dosage compensation.

I think that if Muller had been receptive to the obvious implications of the salivary gland measurement studies for the mechanism of dosage compensation, the *Drosophila* field might have progressed more rapidly and his influence enhanced.

The excitement and interest over Lyon's work was apparently not because it explained mammalian dosage compensation. Rather, it was of the unique mechanism involved, distinguishing permanently in somatic inheritance between the behaviour of two X chromosomes in the same cell. Mary Lyon's work, however, did have a tremendous impact on the subject of mammalian dosage compensation, and probably restarted a major interest in *Drosophila* dosage compensation as well.

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