THE APPLICATION OF THE MAIZE-DERIVED GENE COMPETITION MODEL TO THE PROBLEM OF DOSAGE COMPENSATION IN DROSOPHILA

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ABSTRACT

The gene competition model, originally formulated from studies on the regulation of alcohol dehydrogenase activity in maize, is also applicable to the phenomenon of dosage compensation in Drosophila. The model accounts for the absence of dosage compensation in sex determination.

FOLLOWING the formulation of the gene competition model in our laboratory, it became clearly evident that this model could account for the phenomenon of dosage compensation of *X*-linked genes in Drosophila. One of the basic tenets of the competition model for the genetic control of ADH in maize (SCHWARTZ 1971) is that total gene activity may be independent of gene dosage and be determined by the concentration of regulatory factors which are involved in gene transcription. Recently published studies on dosage compensation (LUCCHESI and RAWLS 1973; MARONI and PLAUT 1973) provide additional support for this hypothesis. *X*-linked sex-determining genes in *Drosophila melanogaster* do not show dosage compensation. The purpose of this communication is to point out how the maize-derived regulatory model is also applicable to the Drosophila situation.

The phenomenon of dosage compensation of *X*-linked genes is well documented. Comparisons of gene function, both at the level of RNA synthesis (MUKHERJEE and BEERMANN 1965; MARONI and PLAUT 1973) and of enzyme action (GRELL 1962; SEECOF, KAPLAN and FUTCH 1969; TOBLER, BOWMAN and SIMMONS 1971; BAILLIE and CHOVNICK 1971; LUCCHESI and RAWLS 1973) in diploid males, diploid and triploid females, and intersexes confirmed MULLER's (1932, 1950) hypothesis that the activity of a gene on an *X* chromosome depends upon the ratio of the number of *X* chromosomes to sets of autosomes. On a per-gene basis, activity in normal 1X:2A males is twice that in 2X:2A or 3X:3A females; and in 2X:3A intersexes it is 1½ times the female level. A constant relation between productivity of *X*-linked and autosomal genes is maintained in spite of variations in the X:A ratio.

Dosage compensation appears to operate at the chromosome and not at the gene level. When the number of *X* chromosomes varies as in the above examples, specific *X*-linked genes exhibit a compensating adjustment in their function. However, when the number of *X* chromosomes and sets of autosomes is kept

constant, there is no compensation and activity is directly correlated with the number of gene copies (LUCCHESI and RAWLS 1973). One class of *X* chromosome genes must be exempt from control by dosage compensation, namely those involved in sex determination. In Drosophila, it is postulated that sex is determined by the balance between genes for maleness in the autosomes and those for femaleness carried on the *X* chromosome (BRIDGES 1925). If the female determining genes on the *X* were twice as active in the male as in the female, there would be no difference in the sexes. The question at hand is why are certain genes in the *X* twice as active in the male as in the female, while those genes in the *X* involved in sex determination do not show dosage compensation. The mechanism responsible for dosage compensation must account for these facts as well.

The gene competition model proposes that gene transcription is mediated by some factors which occur in limiting concentrations. These factors may be specific DNA-dependent RNA polymerases, sigma-like factors which confer specificity to the polymerases (BURGESS *et al.* 1969), or the like. Specific factors are involved in the transcription of groups of genes (with similar promoters). Factor concentration is limiting; hence the rate of transcription of each group of genes will depend on the concentration of the factor rather than on gene dosage. Dosage compensation will result if the limited factors are specified by autosomal genes and if *all* the genes which comprise a single group (i.e., transcribed by the same limited factor) are located either on the *X* chromosome or the autosomes. A similar scheme was recently suggested by MARONI and PLAUT (1973). As long as comparisons are between flies with normal chromosomes that contain complete sets of genes, function of X-linked genes will be independent of gene dosage. In males, all of the molecules of a specific factor are used in the transcription of a group of genes on the *X*. In 2*X* females, the same molecules, in the same concentrations, are used to transcribe twice as many genes. However, since the factor concentration is limiting, identical numbers of m-RNA molecules are produced in the 1*X* male and in the 2*X* female. The dosage of a particular *X*-linked gene will not affect the total amount of gene product as long as its proportionate representation among the other genes in the group remains constant. The activity of an *X*-linked gene will depend upon its dosage in relation to that of other genes within the group and not on the number of *X* chromosomes. This hypothesis is consistent with the results of LUCCHESI and RAWLS (1973) who found no dosage compensation when the dosage of a gene was changed but the number of *X* chromosomes was held constant. Consider the following hypothetical situation. *Pgd* is one of five *X*-linked genes in group I which are transcribed by a particular autosomally specified factor. Assume each autosomal gene produces 25 factor molecules per cell. With 50 factor molecules, 50 nascent m-RNA molecules can be simultaneously transcribed on group I genes. In the males these are distributed among the five genes on the single *X* chromosome with 10 nascent m-RNA molecules on each gene. At any one time 10 *Pgd* messages are being made. In the 2*X* female the 50 nascent m-RNA molecules are transcribed on two sets of group I genes but 10 *Pgd* messages are also made in the female at any one time, since there are two *Pgd* genes in the diploid female. Thus, total *X*-linked gene activity is constant in male and female and independent of the number of *X* chromosomes.

Triploid females will have 75 factor molecules involved in the transcription of 75 m-RNA molecules on the three *X* chromosomes, 15 of which are *Pgd* messages. Five *Pgd* messages will be transcribed on each *X* chromosome both in diploid and triploid females. Now consider the consequences of changing the *Pgd* dosage while the number of *X* chromosomes is held constant by use of a gene duplication in a diploid female. The 50 factor molecules will transcribe 11 genes, three of which are *Pgd*. An average of 4.5 m-RNA molecules will be transcribed on each gene, but in agreement with the results of LUCCHESI and RAWLS (1973), there will be an increase in the number of *Pgd* messages: 13.5 as compared to 10 in a normal diploid female.

No specific genes for maleness or femaleness have been isolated; however, the *X* chromosome must carry genes which play a role in sex determination, since sex is governed by the balance between the *X* chromosome and the autosomes. The absence of dosage compensation in the control of *X*-linked genes involved in sex determination can be readily accounted for on the competition model by postulating that the *X*-linked and the autosomal sex genes are in a single group and are transcribed by the same factor. Under these conditions relative gene expression will depend on the *X*:autosome ratio. The genes for femaleness on the *X* and for maleness on the autosomes will compete for the same limited factor molecules. In females with 2*X* chromosomes more of the factor molecules will be used in transcribing genes for femaleness than in males with only 1*X*.

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