ed with probability, \( p = 1 - e^{-\lambda x} \), so that the expected number of collisions is \( np \) and variance is \( np(1 - p) \) \[ R. Pyle, J. R. Stat. Soc. B 27, 395 (1965). \] Our data suggest that 13 out of 17 (76%) adenomas were polycional. We observed approximately 300 polyps in a colon length of 15,000 crypts. The mean width of the observed adenomas was seven crypts (although this figure is an overestimate of \( x \), because it was observed after any collisions had occurred, which presumably had the effect of increasing \( x \)). We analyzed the model assuming different values of \( n \) and determining whether these values can account for two observations: (i) the final figure of 300 adenomas after any collisions have occurred, and (ii) the estimate of 76% polycionality. In general, it is not possible to reconcile observations (i) and (ii). If \( n \) is sufficiently small to account for observation (i), then far too few collisions occur to account for observation (ii). Conversely, if \( n \) is large enough to account for observation (ii), then many more polyps than 300 result. For example, use an estimate for \( n \), assuming that each polyclonal adenoma is formed of three original adenomas. In this case, \( n = 756, x = 7, \) and \( y = 15,000 \). Then, it follows that \( p = 0.297; np(1 - p) \) (variance in the number of collisions) = 157 (SD = 12.5); and \( n(1 - p) \) (number of noncollision polyps) = 531. If each collision involves a mean of three adenomas, then 225/3 = 75 polyclonal adenomas result (12.4% of total) and a total of 606 adenomas is predicted. Even if the number of collisions is increased by 2 SD (\( \pm 5\% \) confidence limit) from the 225 predicted, the total number of polyps resulting is 590, which is far in excess of 300. Moreover, in order to account for the observation that 13 out of 17 adenomas were polycional, given that 12.4% of all polyps is polycional, the appropriate terms in the binomial distribution \( p = 0.124, n = 17 \) are calculated to give \( P \) (observed polycionality) \(< 3 \times 10^{-6} \). Thus, the model suggests that the collision hypothesis cannot account for the observed data.

For mixed (XO/XY) adenomas, mean width = 5.93 crypts (\( n = 13 \)); and for all adenomas, mean width = 6.82 (\( n = 285 \)) and SEM = 0.554. The width of mixed adenomas does not differ significantly from that of the general polyp population (normal distribution, two-tailed test, \( P > 0.1 \)).

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Thus, our explanation, based on gene expression data, proposes a single mechanism of dosage compensation for all X chromosome genotypes with modification by the sex determination mechanism and accommodates the localization of the MSL proteins to the X chromosome in males.

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REFERENCES AND NOTES

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Response: Because of space limitations, we only briefly referred to the trans-acting inverse dosage effects theory for dosage compensation favored by Birchler and his co-workers (1). The controversy can be distilled down to whether the primary defect in msl mutant males is an inadequate amount of X-encoded gene products or an excess of autosomally encoded products. Our understanding of Birchler's model is
that males (1X:2A) have a natural tendency to hypertranscribe many genes in the genome because of the absence of one copy of the X chromosome. In his model, the msl wild type gene products nullify the inverse effect on the autosomes (1), in contrast to the "X chromosome model," in which the MSL proteins primarily affect transcription of the X and not the autosomes (2). In his comment, Birchler suggests how the MSL proteins might regulate the autosomes in spite of their physical location on the X chromosome. In his inverse effect model, the primary function of the MSL complex is to sequester a hypothetical factor mediating the inverse effect away from the autosomes, thus reducing their expression to basal level. One of the reasons we prefer the X chromosome model is that removing the MSL complex in mutant males, or ectopically expressing the MSL complex in females, produces gross alterations in X chromosome morphology consistent with altered transcriptional levels, but does not affect autosome morphology (3).

The basis for the disagreement lies in the difficulty of identifying primary (as opposed to secondary) effects in mutants, compounded by the great technical challenge of directly measuring small changes in transcription. The foundation of the inverse effect model depends on precise measurements of steady state RNA concentrations or enzymatic activities in dying individuals. The validity of the measurements becomes even more tenuous when adults rather than larvae are studied, because these are rare, atypical escapers. Thus, the variable gene expression Birchler and colleagues found for both X-linked and autosomal genes could be attributed to the gross pathology of dying cells, which have altered molar ratios of X and autosomally encoded transcription factors (1). Furthermore, the deletion of a large chromosome segment or the failure to dosage compensate the male X could reduce certain transcription factors or other chromatin proteins by 50%, and this could secondarily alter expression of the remaining genome in unpredictable ways, either positively or negatively.

Although similar criticisms may be made of expression studies supporting the X chromosome model for dosage compensation, we are basing our support of this model largely on the X chromosome localization of the MSL proteins and X chromosome morphology in msl mutants. These observations strongly favor the hypothesis that the MSL proteins primarily function to increase X-linked gene expression.

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REFERENCES

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