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Editorial

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Solving the Mystery of the Evolution of X Chromosome Inactivation

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The X chromosomes of therian (marsupial and eutherian) mammals share a common evolutionary origin, with the marsupial X corresponding to approximately two-thirds of the human X chromosome [1]. Inactivation of the X chromosome in female somatic cells is observed in both of these mammalian lineages and is presumed to have evolved in the therian ancestor to compensate for X-gene dosage differences between XY males and XX females. In the 50 years since Mary Lyon's landmark publication on the hypothesis of X chromosome inactivation (XCI) [2], we are still struggling to unravel the evolution of this fascinating silencing mechanism. A lack of comparable data from distantly related mammalian species has made it difficult to determine the evolutionary history of this silencing mechanism. Fortunately, a series of recent studies has provided this much needed data. Do the hypotheses regarding the evolution of XCI hold up in light this new data?

Ohno [3] proposed that dosage compensation for X-borne genes required upregulation to restore the X to autosome transcription ratio to one in males. This in turn led to an overexpression of X-borne genes in females, which was counteracted by XCI. A recent test of Ohno's hypothesis using RNA-seq data suggests that in the seven eutherians species studied (6 primates and mouse); the X chromosome is not up-regulated [4] and therefore, may not be the driving force behind the evolution of X chromosome inactivation. However, the marsupial X does appear to have some level of up-regulation and they appear to have efficient dosage compensation between males and females [4]. This means that either the ancestral therian X chromosome was originally up-regulated in males, with this being maintained in the marsupial lineage but lost in the eutherian lineage or alternatively, this mechanism independently evolved in marsupials. Examining the average gene expression in a population of cells does provide some important insight but also has its limitations. It is important to keep in mind that this data was obtained from tissues consisting of heterogeneous cell populations, with potentially different expression profiles for different cell types. Therefore, we need to understand what is happening in individual cells.

By using RNA-FISH, a technique that permits the visualization of X-borne gene primary transcripts in single cells, it is evident that there are similarities between marsupials and eutherians. Genes on the marsupial X show a reproducible frequency of cells with monoallelic or biallelic expression [5]. This was also observed for genes escaping inactivation in three distantly related eutherian species (human, mouse and elephant) [6], particularly for genes in the region added to the X chromosome in the eutherian lineage. This is similar to the pattern of expression observed for genes on the multiple X chromosomes of a monotreme mammal, the platypus, the X chromosomes of which share no homology to the therian X [7]. It has been proposed that this type of probabilistic expression represents an ancient method of silencing from which XCI arose [8]. This mechanism has been independently exapted for X-gene silencing in the monotreme and therian lineages. Comparisons between marsupials and eutherians of epigenetic marks on the X chromosome further support the idea of a common origin of XCI, with both lineages possessing marks of active chromatin. Consistent with the more tightly controlled inactivation observed in individual nuclei [6] eutherians have addition marks that appear to modify the inactive X [9].

Comparisons of distantly related species suggest that there are some common features of XCI between both lineages and support the idea of a common origin of XCI. However, in light of the recent expression analysis using RNA-seq, the driving force behind the evolution of XCI is brought under scrutiny. Was dosage compensation the driving force behind XCI or has this logical hypothesis led to the dismissal of alternative hypotheses? Future research should continue to compare XCI in diverse species, if we are to unravel the mysteries behind the evolution of this remarkable epigenetic mechanism.

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