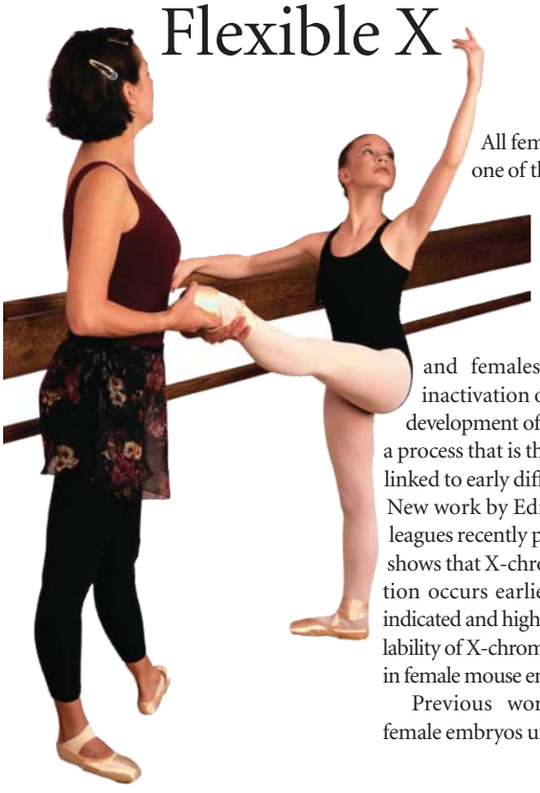
CHROMOSOME IMPRINTING

# Flexible X



All female mammals have one of their two X chromosomes randomly inactivated in every somatic cell to ensure that X-linked gene dosage is equal in males and females. X chromosome inactivation occurs during early development of female embryos, in a process that is thought to be tightly linked to early differentiation events. New work by Edith Heard and colleagues recently published in *Science* shows that X-chromosome inactivation occurs earlier than previously indicated and highlights the surprising lability of X-chromosome inactivation in female mouse embryos.

Previous work indicated that female embryos undergo three waves of X-chromosome inactivation, which correlate with the three earliest differentiation steps. The first two lineages to differentiate are the trophectoderm and the primitive endoderm, which give rise to extra-embryonic lineages. Normally, the paternal X chromosome (Xp) is inactivated in these two lineages. This occurs as a result of an imprinted predisposition of Xp to inactivate, and an imprinted resistance of the maternal X chromosome (Xm) to inactivate. The third wave of differentiation involves epiblast cells from the inner cell mass (ICM), where X-chromosome inactivation is random. Both imprinted and random inactivation of X chromosomes involve *Xist*, a unique un-translated RNA that coats the X chromosome to induce silencing. *Xist* is expressed from the two- to four-cell stage onwards, with early expression from the *Xp* locus only.

To further understand the kinetics of imprinted X-chromosome inactivation during early development, Heard and colleagues used a combination of RNA fluorescence *in situ* hybridization (FISH) and immunofluoresence at the single-cell level to examine *Xist* expression and Xp-chromosome inactivation. Xp-chromosome inactivation can be measured by studying the enrichment of proteins that are involved in X-chromosome inactivation, such as H3 histone methylase and the polycomb proteins Eed/Enx1, as well as through RNA polymerase II activity, characteristic histone modifications and nascent transcript detection of an X-linked gene. These studies indicate that Xp is rapidly inactivated at the four-cell stage. At the 32-cell stage, Xp is inactivated in nearly all cells, and this is maintained in the trophectoderm and primitive endoderm. However, during ICM growth, Xp inactivation is reversed and cells rapidly lose the *Xist* coating, Eed/Enx1 enrichment and histone modifications that are characteristic of the inactive state from the Xp chromosome. Reversal of Xp inactivation allows random activation of either the maternal or paternal X chromosome in epiblast cells following implantation. This indicates the highly labile state of Xp during

early development and shows that the ICM is crucial for the reversal of Xp inactivation.

Why mouse embryos show this dynamic inactivation of Xp is unclear, although it might be a solution to parental genome conflict. This remarkable flexibility of the Xp chromosome during pre-implantation development highlights the importance of the ICM in reprogramming epigenetic marks in early embryonic development.

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## References and links

**ORIGINAL RESEARCH PAPER** Okamoto, I. *et al.* Epigenetic dynamics of imprinted X inactivation during early mouse development. *Science* 17 Dec 2003 (doi:10.1126/science.1092727)

**FURTHER READING** Reik, W. & Walter, J. Genomic imprinting: parental influence on the genome. *Nature Rev. Genet.* **2**, 21–32 (2001) | Wilkins, J. F. & Haig, D. What good is genomic imprinting: the function of parent-specific gene expression. *Nature Rev. Genet.* **4**, 359–368 (2003)

**URL**

LocusLink:
http://www.ncbi.nlm.nih.gov/LocusLink

Xist
http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=213742