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# X-inactivation and Epigenetics

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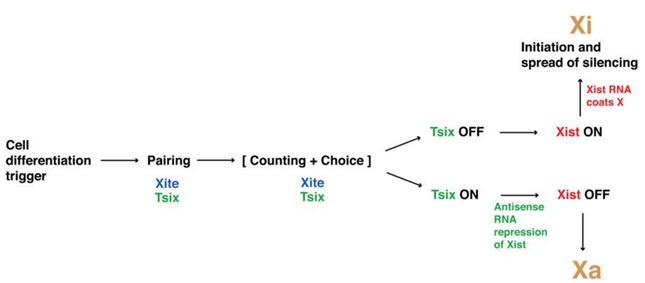
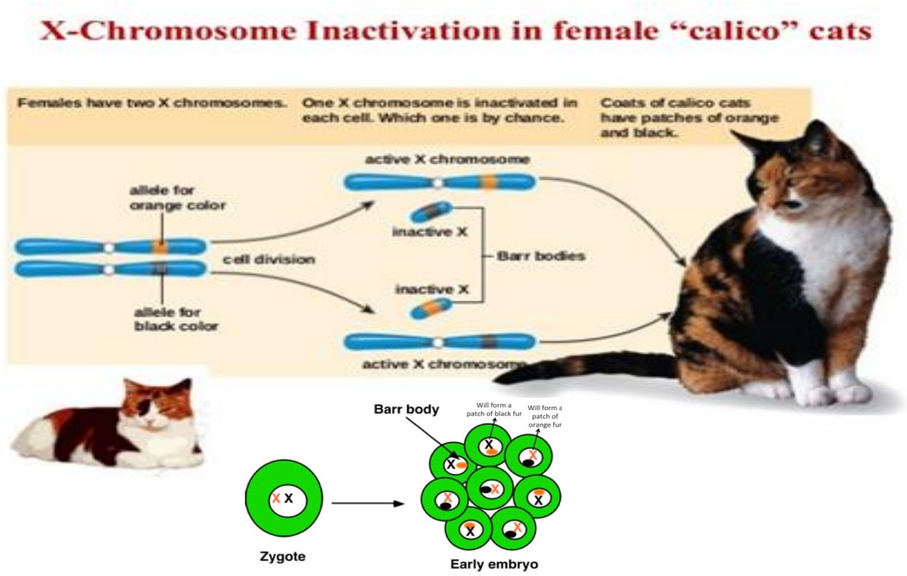
## Abstract:

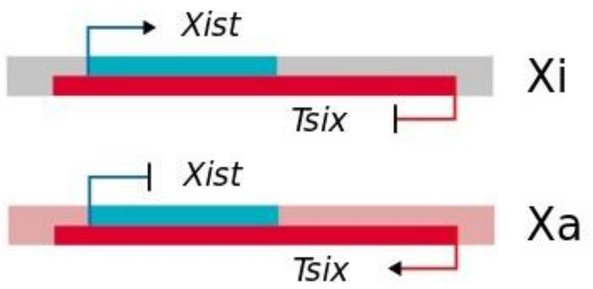
**To prevent abnormal development caused by expressing two X chromosomes, female mammals use an epigenetic process called dosage compensation, which involves one of their X chromosomes being inactivated. X chromosome inactivation (XCI) occurs during the formation and development of an embryo. XCI involves the condensing of DNA, which is marked by the change in histone tail modifications, arrival of structural proteins, and DNA methylation. The result is the formation of extraordinarily stable heterochromatin.**

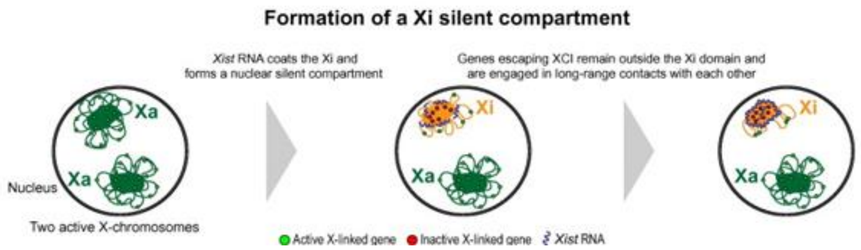
**X-inactivation is regulated in cis by the X-inactivation center (Xic), which contains the Xist gene and its antisense gene, Tsix. Xic actions occurs when there is change in Xist RNA from unstable to highly expressed. Xist RNA coats the future inactive X from which it is expressed. Xist RNA is required for the recruitment of epigenetic regulators, Polycomb Repressive Complexes PRC1 and PRC2 which catalyze the deposition of H2AK119 ubiquitination and H3K27 trimethylation respectively. These events eventually lead to the X chromosome being condensed into a small, cluster of DNA called a Barr Body. By packing the DNA this way, it is silenced. Calico cats get their beautiful color patches this way. The gene responsible for fur color is on the X chromosome. Some cells inactivate the X chromosome carrying the black fur allele and others inactivate the X chromosome carrying the orange fur allele. The patches are formed from millions of cells expressing either the black or orange fur allele, all of which stemmed from one of the parental cells.**

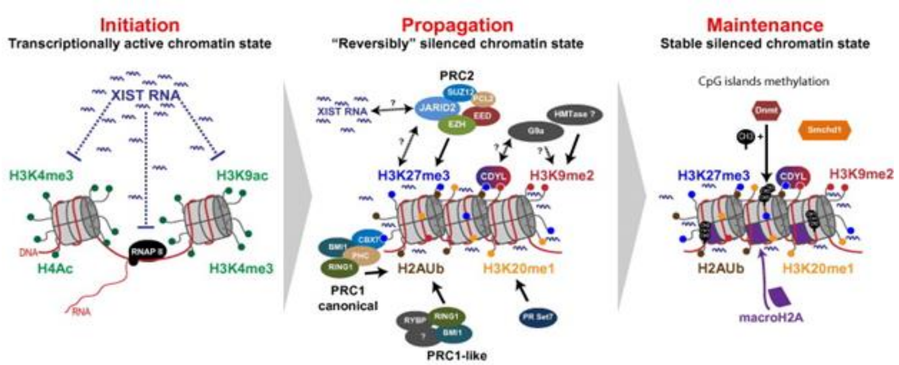
***Xist* is the critical determinant for X-inactivation. *Xist* is a 17kb, spliced, and polyadenylated long non-coding RNA. The lncRNA, Xist, and its antisense, Tsix, are cis acting factors in the X-inactivation center (XIC) and initially transcribed from both X chromosomes. Tsix is turned off on one of the X chromosomes that then accumulates Xist transcripts and becomes the inactive X. In contrast, Tsix transcription persists longer on the other X, on which Xist is then turned off, enabling it to become established as the active X. Because of this dynamic and complementary relationship, Tsix has been proposed to be the regulatory "switch" that determines whether Xist is on or off and thus whether the X becomes the inactive or active X. Hence the palindrome... Tsix on, no Xist!**


## There are specific stages of X-inactivation:

**Counting: There is only one X chromosome that remains active per diploid set of autosomes. The cell must have a mechanism to count how many X chromosomes there are in relation to how many autosomes.**

**Choice: Imprinted X-inactivation (mice and marsupials) predetermined paternal X chromosome is inactivated. Random X-inactivation (eutherian mammals) randomly choose one of the X chromosomes per cell to be inactivated**

**Initiation: Once XCI is initiated, a series of events takes place which changes the euchromatin of the active X chromosome into the tightly packed inactive heterochromatin of the Xi, which can be recognized as the Barr body in female somatic cells. Xist is expressed in *cis* from the future inactive X (Xi) and its expression is the first detectable event in X-inactivation. The loss of euchromatin-associated histone modifications such as H3K9 acetylation and H3K4 mono- and di-methylation are among the earliest chromatin changes that occur following Xist RNA coating. In addition, the disappearance of factors associated with transcription, such as RNA polymerase II and loss of nascent transcripts are also observed on the Xi immediately after Xist coating, which leads to an immediate reduction of gene transcription on this chromosome and the creation of a silent nuclear compartment, initiating X-linked gene-silencing. One or two cell cycles later, several new histone modifications such as H3K27 tri-methylation (H3K27-me3), H3K9 di-methylation (H3K9-me2), and H4K20-mono-methylation (H4K20- me1) appear on the Xist-coated chromosome. The new histone modifications recruit both Polycomb Repressive complexes, PRC1 and PRC2, to the Xi either directly or indirectly, which help with the formation of the heterochromatin.**

**Maintenance: the role of DNA methylation, of the dinucleotide CpG is to "lock in" the heterochromatin, eliminating the cell's ability to transcribe the DNA.**

**X inactivation doesn't happen instantly but instead happens progressively over a period of developmental time. X inactivation is accomplished via a progressive accumulation of redundant epigenetic marks on the inactive X chromosome which ensure the incredible stability of this mitotic heritability for the life time of a female organism.**

*Figures Courtesy of:* J. Lee / Genes &Development 23 (2009) 1831-1842, *www.slideshare.net/genetics,* *www.acsh.org/news/calicocatsareawalkinggeneticlesson*, *www.wikimedia.com*, R. Chaligné, E. Heard / FEBS Letters 588 (2014) 2514–2522

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Chaligné, R., Heard, E.(2014). X chromosome and development in cancer. *FEBS Letters* 588: 2514–2522
Willard, H.F., Carrel, L. (2001). Making sense (and anti-sense) of the x inactivation center. *PNAS vol.98 no.18 10025-10027*

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