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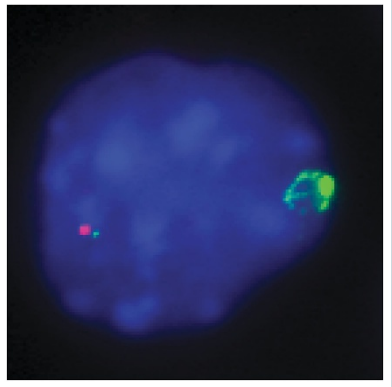
Keeping the right dosage

Sex chromosomes present a gene expression dosage problem for the organisms that carry them: if the male is XY and the female XX, the female has a double dose of X chromosome genes. This has been overcome in very different ways in different organisms: whereas *Drosophila melanogaster* doubles gene expression from the single X chromosome in males, vertebrates take a different approach, controlling gene expression by inactivating one of the two X chromosomes in the female. Noncoding RNAs have been implicated in the mechanism of dosage compensation in both cases, but although there are many potential *cis*-elements that may be involved in mammalian X chromosome inactivation, the order and mechanism by which they act are still being elucidated. To further complicate the issue, mammals have two modes of X chromosome inactivation. In the placenta, the paternal X chromosome is always inactivated, in so-called 'imprinted X inactivation', whereas in the embryo, one of the two X chromosomes is randomly inactivated. In recent work from Lee and colleagues (*Dev. Cell* **12**, 57–71, 2007), a common layer of upstream regulation has been found to control X chromosome inactivation in mammals. The authors discovered that a repeat element regulates X chromosome inactivation in the context of both imprinted and random inactivation.



A single locus, *Xic*, is known to regulate both the 'counting' of X chromosomes and the subsequent silencing of one chromosome. Several factors encoded at this locus have been implicated in X inactivation in the past, including the noncoding RNA *Xist*, which is expressed from and coats the inactive X chromosome. A second important transcript is the antisense version of this RNA, *Tsix*, which is expressed from the active X and antagonizes *Xist*. A *Tsix* promoter has been defined, but the results of two targeted deletions made by Lee and colleagues now indicate that this region is dispensable for *Tsix* expression and X chromosome inactivation. As a larger deletion more strongly depletes *Tsix* expression, it seems that a different sequence is driving *Tsix* expression. The authors thus focused on the nearby *DXPas34* repeat element and found that it is related in sequence to retrotransposon elements, suggesting its evolutionary origin in an endogenous retrovirus element (ERVL). Using a reporter construct, Lee and colleagues further show that *DXPas34* acts as a bidirectional promoter that is active in embryonic stem cells but not in more differentiated cells (and thus is less active in increasingly differentiated cells, as expected of an element involved in X inactivation).

To test whether *DXPas34* is required for *Tsix* expression (and thus usually antagonizes X inactivation), the authors generated a targeted deletion of this element on one X chromosome and found that *Tsix* expression is specifically lost from that chromosome. The chromosome carrying the *DXPas34* deletion also has higher transcription of genes usually expressed from the inactive X, and is biased towards inactivation, as assessed by Xist co-localization; in contrast, the intact X chromosome (red spot) was not coated with *Xist* (larger green patch) in 80% of cases, suggesting that it is active. This phenotype supports the idea that the intact *DXPas34* element antagonizes inactivation on the active X. Aberrant later expression of *Tsix* from the inactive X in the *DXPas34* deletion strain suggests that the maintenance of silencing is also dependent on this repeat.

In addition to its involvement in random X inactivation, the authors also have evidence suggesting that imprinted silencing is affected by *DXPas34*. They found that deletion of this locus on the maternal X chromosome is embryonic lethal, whereas embryos lacking this locus on the paternal X are unaffected. Although the mechanism of *DXPas34* action in this context is unclear, this result indicates disruption of imprinted X inactivation.

Overall, this work suggests that *DXPas34* acts upstream to enhance *Tsix* expression and downstream to maintain *Tsix* silencing, and it also begins to reveal which previously implicated elements ultimately contribute to the regulation of *Xist* expression. Furthermore, the study indicates that imprinted and random X inactivation share a common upstream element in their regulation. This opens the door to further understanding inactivation through identification of the factors that regulate *DXPas34* and the molecular mechanisms by which it acts to enhance and silence gene expression. ***Sabbi Lall***