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CHROMATIN

Xist as a recruitment tool


Robert Decelis Ltd/Stone/Getty

In female mammals, one of the two X chromosomes is transcriptionally silenced in a process called X chromosome inactivation (XCI). A study published in *Science* provides important new insights into the mechanisms that underlie this process, identifying a new role for the long non-coding RNA (lncRNA) Xist in mediating DNA structural changes that, in turn, facilitate transcriptional silencing.

Xist was known to spread along the X chromosome to silence transcription through the exclusion of RNA polymerase II. This is associated with recruitment of the X chromosome to the nuclear lamina and large-scale chromosome remodelling, but the importance of these structural changes was unclear. Chen *et al.* reasoned that a recently identified interaction between Xist and the nuclear lamina protein lamin B receptor (LBR) could be required for structural remodelling and transcriptional silencing. To test this idea, they disrupted the Xist–LBR interaction in mouse embryonic stem cells by knocking down LBR expression or deleting key binding motifs within LBR or Xist. This resulted in defective transcriptional silencing that could be rescued by artificially tethering Xist to LBR, demonstrating that the Xist–LBR interaction is required for the silencing of gene expression during XCI.

Next, they assessed the role of this interaction in the recruitment of the X chromosome to the nuclear lamina, by fluorescently visualizing the Xist-coated nuclear compartment (surrounding the *Xist* gene on the X chromosome) and lamin B1 (LMNB1) a nuclear lamina component. In wild-type cells, the *Xist* compartment overlapped with the nuclear lamina, whereas in cells with disrupted Xist–LBR binding, the distance between the two regions was 20-fold greater. Artificially tethering Xist to LBR or LMNB1 restored localization of the Xist compartment to the nuclear lamina and transcriptional silencing, demonstrating that recruitment to the nuclear lamina, mediated by the Xist–LBR interaction, is required for transcriptional silencing of the X chromosome.

The researchers proposed that lamina recruitment might reposition actively transcribed genes on the X chromosome that is undergoing silencing to within the Xist-coated nuclear compartment, allowing Xist to spread. Consistent with this, in the absence of LBR, Xist was excluded from all actively transcribed genes on the X chromosome. In addition, an active gene (*Gpc4*) on the X chromosome was located far from the Xist-coated nuclear compartment, similar to an autosomal gene (*Notch 2*). By contrast, in wild-type cells *Gpc4* overlapped the Xist-coated nuclear compartment, suggesting that the Xist–LBR interaction allows actively transcribed genes to be repositioned there.

The authors propose a model in which Xist, initially bound to DNA sites near its own gene, tethers the X chromosome to the nuclear lamina through its interaction with LBR. This constrains the DNA such that Xist-coated regions are positioned away from the actively transcribed *Xist* gene and non-coated regions are brought closer to it, facilitating the spread of Xist and ultimately silencing the entire chromosome.

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> “recruitment to the nuclear lamina, mediated by the Xist–LBR interaction, is required for transcriptional silencing of the X chromosome”

ORIGINAL ARTICLE Chen C.-K. *et al.* Xist recruits the X chromosome to the nuclear lamina to enable chromosome-wide silencing. *Science* http://dx.doi.org/10.1126/science.aae0047 (2016)