Revealing a missing link

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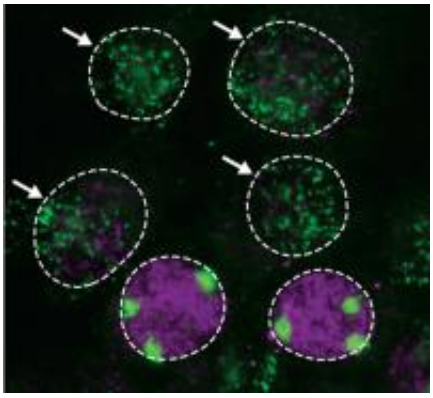

Fluorescence experiments in mouse cells demonstrate that hnRNP U expression is essential to the proper localization of Xist RNA. Arrowheads indicate cells with reduced expression of hnRNP U (purple), resulting in diffuse distribution of Xist (green) rather than the tight X chromosome-associated clusters seen in cells expressing hnRNP U (purple). Credit: 2010 Shinichi Nakagawa

When it comes to genes, it's definitely possible to have too much of a good thing. Accordingly, mammalian females have a mechanism that randomly inactivates one of the two X sex chromosomes within each somatic cell nucleus, ensuring that X-linked genes are represented to the same extent as in their single-X-bearing male counterparts.

This process is executed by the product of the *Xist* gene. Although messenger RNAs typically get exported to the cytoplasm to produce protein, Xist RNA remains in the nucleus and accumulates along the surface of the X chromosome that is to be inactivated, and new findings

from a team led by Shinichi Nakagawa at the RIKEN Advanced Science Institute in Wako have provided valuable insights into the mechanism behind this unusual localization.

Their screen of RNA-binding factors revealed a central role for heterogeneous ribonuclear protein U (hnRNP U) in regulating Xist distribution, and this RNA was scattered diffusely throughout the nuclei of cells in which hnRNP U levels were artificially reduced. Closer analysis indicated that hnRNP U acts as an intermediary that binds directly to both RNA and chromosomal DNA and tethers the two together. This physical association appears to be essential to X inactivation; although mouse embryonic stem cells lacking hnRNP U successfully initiated the maturation process, they were significantly more likely to exhibit gene activity from both X chromosomes.

Previous investigations have identified a structural role for hnRNP U within the nucleus, and at least one group has demonstrated that this protein tends to cluster near X chromosomes, although this potential aspect of its function remained unaddressed for the better part of decade. Indeed, Nakagawa was taken aback by its involvement in X inactivation. “I was surprised that we came across a factor that has been well-studied in the field of molecular biology rather than a ‘novel’ gene,” he says.

Although Xist is unique in its capacity to engineer the shutdown of an entire chromosome, there are numerous other non-protein-coding RNAs that contribute to the regulation of gene activity at a far smaller scale. Nakagawa hopes that this study will offer a window onto those mechanisms as well. “In most cases these non-coding RNAs control neighboring genes on the same chromosome, in a similar manner to Xist,” he says, “and it is possible that these non-coding RNAs are, in general, also retained around the site of transcription by hnRNP U.”

More information: Hasegawa, Y., et al.The matrix protine hnRNP U is required for chromosomal localization of Xist RNA. *Developmental Cell* 19, 469–476 (2010). Article

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