URLs

X INACTIVATION

Imprinted inactivation: narrowing down the options

Studies in mice have been fundamental in understanding mammalian X-chromosome inactivation, but there are still important gaps in our knowledge of some of the processes that are involved. One of the missing pieces of the puzzle is how the imprinted X inactivation that takes place early in mouse development — before the onset of random inactivation — is initiated. Edith Heard and colleagues have now narrowed down the possibilities by ruling out one plausible mechanism.

In imprinted X inactivation, the paternally derived X chromosome (Xp) is silenced in all cells. One theory about how this silencing occurs is that Xp is pre-inactivated in the male germ line. In spermatocytes, the X and Y chromosomes are transcriptionally silenced in a process that is known as meiotic sex-chromosome inactivation (MSCI). Could the inactivation of Xp at this stage be carried over after fertilization?

Heard and colleagues tested this possibility in mice by examining the behaviour of a transgene that carries the gene X-(inactive)-specific transcript (*Xist*) — which is required in *cis* for X inactivation — and its surrounding sequences. When inserted into an autosome and inherited paternally, this transgene is inactivated during early development and shows epigenetic and replication-timing features that are similar to Xp, which indicates that it contains all the *cis* sequences that are necessary for imprinted X inactivation.

But can this inactivation be explained by MSCI? In spermatocytes, chromatin marks that are typical of MSCI were absent from the transgene, which was also transcriptionally active, unlike Xp. Moreover, inability to undergo pairing during meiosis does not seem to have a role in inactivation: the transgene was inactivated whether it was inherited from males that were hemizygous or those that were homozygous for the autosome that carried it.

Gene-expression studies also argued against a role for MSCI in establishing imprinted inactivation as it seems that silencing of Xp genes takes place in the embryo itself, and not before fertilization. Cysteine-rich hydrophobic domain 1 (*Chic1*), which is ultimately silenced on the inactive X chromosome, was initially expressed from both Xp and the *Xist* transgene in the early mouse embryo, and only became silenced from the 8-cell stage onwards. Similar patterns were seen for global transcription from the Xp and the transgene-carrying autosome.

So what event triggers imprinted inactivation early in embryogenesis? Heard and colleagues showed that only low levels of *Xist* mRNA are expressed from Xp at the 2-cell stage, and the transcript only later accumulates on the chromosome. This indicates that it might be *de novo* expression of the *Xist* transcript from Xp that initiates imprinted inactivation.

While ruling out MSCI as the cause of imprinted X inactivation, this study leaves important questions open. What leads to the expression of *Xist* from Xp early in development? And why is the maternal allele repressed? Whether a feature of the male germline other than MSCI is involved or a different mechanism entirely is operating awaits further investigation.

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References and links

ORIGINAL RESEARCH PAPER
Okamoto, I. *et al.* Evidence for *de novo* imprinted X-chromosome inactivation independent of meiotic inactivation in mice. *Nature* 16 October 2005 (doi:10.1038/nature04155)

FURTHER READING Reik, W.& Lewis, A. Co-evolution of X-chromosome inactivation and imprinting in mammals. *Nature Rev. Genet.* **6**, 403–410 (2005) | Huynh, K. D. & Lee, J. T. X-chromosome inactivation: a hypothesis linking ontogeny and phylogeny. *Nature Rev. Genet.* **6**, 410–418 (2005)