Understanding X-chromosome silencing in humans

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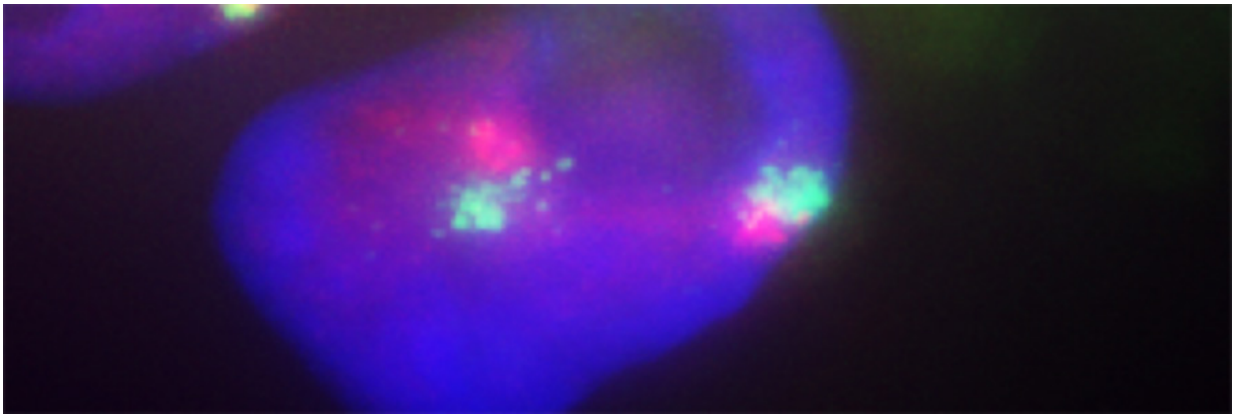

Use of the RNA-FISH visualisation technique reveals co-accumulation of XIST (green) and XACT (red) on the two active X-chromosomes in female 'naïve' human embryonic stem cells. Image credit: Céline Vallot, Paris Diderot University. Credit: Céline Vallot, Paris Diderot University.

Researchers have discovered new insights into how one of the two X-chromosomes is silenced during the development of female human embryos and also in lab-grown stem cells. X-chromosome silencing is essential for proper development and these findings are important for understanding how the activity of the X-chromosome is regulated to ensure the healthy development of human embryos.

Female cells have two X-chromosomes. One X-chromosome is shut

down in the earliest stages of development preventing the duplicated expression of genes from both X-chromosomes. Previous work using mouse embryos showed that a long RNA molecule called Xist coats regions of the silenced X-chromosome. By latching on to the DNA, Xist recruits proteins that shut down the chromosome. However, although XIST is expressed in human embryos, X-chromosome silencing isn't triggered until a few days later. The different observation in mouse and human embryos suggests that XIST is unable to fulfil the same role in humans as in mouse development. Until now, it was unclear why XIST does not inactivate the X-chromosome in human embryos, or what triggers X-chromosome silencing.

Researchers at the Paris Diderot University, Institut Curie and the Babraham Institute report today in *Cell Stem Cell* that a second long RNA molecule, XACT, which exists in humans but not in mice, accumulates with XIST on active X-chromosomes in human embryos. The two RNAs do not overlap; instead XACT and XIST occupy large and distinct territories on the X-chromosome.

Strikingly, unspecialised 'naïve' human embryonic stem cells show the same pattern of XACT and XIST accumulation on active X-chromosomes, which suggests that this important epigenetic feature of embryo development is conserved in stem cells cultured in the laboratory. By monitoring the artificial induction of XACT activity in stem cells, the researchers suggest that XACT could restrain XIST activity before chromosome silencing occurs. This interference might explain why XIST is unable to shut down the X-chromosome until XACT activity is diminished at later stages of human embryo development.

Dr Peter Rugg-Gunn, an author on the research paper and research group leader at the Babraham Institute, explained: "This important paper might provide the long sought-after explanation for why XIST appears unable

to trigger X-chromosome inactivation during the earliest stages of human development. It exemplifies that mechanisms of epigenetic regulation can vary substantially between species, and that long RNA molecules can contribute to these variations. It is also very exciting that key aspects of X-chromosome regulation appear to be retained in 'naïve' embryonic stem cells because that opens up the possibility of using stem cells to ask new questions about X-chromosome inactivation, such as how XACT might prevent XIST function."

More information: Vallot et al., (2016) XACT Noncoding RNA Competes with XIST in the Control of X Chromosome Activity during Human Early Development, *Cell Stem Cell* DOI: 10.1016/j.stem.2016.10.014

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