PLASTICITY OF THE XIST REGULATORY LANDSCAPE IN PRIMATE EVOLUTION

Evolution of X-chromosome inactivation mechanisms in primates has proven to be significantly more dynamic than previously assumed. A recent study published in Science Advances by Cazottes et al (1) provides a detailed comparative analysis of the X-chromosome inactivation center in humans, rhesus macaques, and marmosets. The authors employed a complex approach, including high-resolution chromatin conformation capture (Capture Hi-C), transcriptome analysis (RNA-seq), and transcript visualization via RNA-FISH.

They discovered that a HERVK family retrotransposon integrated into the X-chromosome inactivation center within the macaque lineage. Using CUT&RUN profiling, researchers identified four CTCF binding sites within this insertion, which establish a new topological boundary in the 3D genome organization. This boundary effectively isolates the neighboring genes *CHIC1* and *NAP1L2* on the active X chromosome from the regulatory influence of the *XIST* domain. To confirm the functional significance of this element, authors utilized the CRISPR-Cas9 system for the targeted deletion of the HERVK insertion. This manipulation led to a "humanization" of the 3D architecture of the locus in macaques and the activation of ectopic contacts. The authors suggest that macaque-specific boundary between chromatin domains on the active X chromosome protects *CHIC1* and *NAP1L2* genes from ectopic interactions with putative enhancers located between the HERVK retrotransposon and the *XIST* gene. This study demonstrates the role of mobile elements as key genome architects capable of reshaping the chromatin landscape.

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