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Autosome inactivation by ectopic *XIST*in differentiated cells

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Summary

Human *XIST*, when integrated into autosomes in a fully differentiated adult human tumor cell line, caused localized chromosome inactivation, counter to all previous concepts of a specific narrow window of opportunity for X-inactivation

Significance and context

Research so far suggests there is only a small window of opportunity during early embryonic development when inactivation of one of the two X chromosomes in female cells can occur. This conclusion is partly based on work in mouse embryonic stem (ES) cells, where fluorescence *in situ* hybridization in newly differentiating female ES cells showed that the *Xist* RNA transcript first accumulated on and then coated the future inactive X chromosome. The current working hypothesis is that this coating recruits repressor protein complexes to inactivate the entire chromosome. Studies using ectopic *Xist* to trigger autosomal inactivation in the mouse were therefore confined to either developing mouse embryos or differentiating mouse ES cells. Hall *et al*. now ask whether a restriction of the investigation of the action of *Xist* to embryonic cells is precluding other possible scenarios, and whether a similar X-inactivation event window applies in humans. They have, therefore, investigated whether ectopic human *XIST* inserted into an autosome in fully differentiated human cells will cause inactivation of that chromosome in *cis*, outside this early embryonic developmental window.

Key results

To keep everything human, Hall *et al.* used the male human sarcoma cell line HT-1080, rather than interspecific hybrid cells that might confuse the issue. They found that the stable integration of full-length human genomic *XIST* into one of the autosomes in one line of HT-1080 cells caused the localized inactivation of that autosome. Autosomal inactivation was measured by the criteria normally used to measure X-chromosome inactivation, namely an apparent Barr body (condensed chromosome), hypoacetylation and late replication of a heterochromatic region, together with local transcriptional silencing at both long and short range. Due to the major chromosomal alteration in this cell line, the site of *XIST* integration could not be definitely assigned to a particular chromosome but Hall *et al*. concluded that it was not on the X or Y chromosomes.

Methodological innovations

Genomic constructs for transfection contained the entire 30 kb human *XIST* gene and approximately 10 kb flanking sequence. After transfection of HT-1080 cells, copy number and site of integration of the sequences were analyzed but did not remain the same over the course of the work. Only the most stably transfected cells survived over the period of the study.

Conclusions

Only one clone displayed stable chromosome inactivation, but because it appeared that only the most stably integrated transgenes survived the course of the research, Hall *et al.* consider it possible that other clones with inactivated autosomes might have existed during the early part of their study. They conclude that a human *XIST* transgene can induce chromosomal inactivation outside the embryonic developmental window normally associated with X-chromosome inactivation. They did not conclude, however, that all adult cells are necessarily competent to support initiation of chromosomal inactivation; rather, they think that some adult cells are better able to respond to inactivation signals than others. For example, enzyme levels involved in X-chromosome inactivation may be lower in some adult cells than in others and lower than those in embryonic cells, and such cells would thus require more time to inactivate a chromosome. Hall *et al*. also conclude that the capacity of cancer cells to remodel chromatin in response to the *XIST* signal might make them closer to early embryonic cells in that respect.

Reporter's comments

Tumor cells display characteristics similar to those of very early embryonic cells: both types of cell are mobile, proliferative and undifferentiated. Genes that are expressed only in early embryonic cells, not in fetal or adult tissues, have also been shown to be activated in tumor cells. Tumor cells may therefore arise from the deprogramming of a fully differentiated adult somatic cell to a more proliferative and multipotent stem-cell state, through the aberrant expression of very early embryonic genes. Thus, a tumor cell is likely to be more similar to an early embryonic cell than to an adult cell. It may therefore not be surprising that a tumor cell line can support initiation of chromosome inactivation apparently outside the normal window for this process.

Table of links

Proceedings of the National Academy of Sciences of the United States of America

References

1. Hall LL, Byron M, Sakai K, Carrel L, Willard HF, Lawrence JB: An ectopic human *XIST* gene can induce chromosome inactivation in postdifferentiation human HT-1080 cells. Proc Natl Acad Sci USA. 2002, 99: 8677-8682.