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RNA BIOLOGY

There's nothing abnormal about chimeric RNA

Chimeric RNAs and the proteins translated from them often have a causal role in tumorigenesis. They are also occasionally found at low levels in healthy cells. These phenomena were previously thought to be exclusively the result of DNA rearrangements, but a new study shows that *trans*-splicing of mRNAs can be a frequent and regulated occurrence in some normal cells.

A chromosomal translocation that joins the first 3 exons of *JAZF1* to the last 15 exons of *JJAZ1* (also called *SUZ12*) has been found in several endometrial cancers, and has been shown to confer resistance to apoptosis when expressed in normal cells. Sklar and colleagues investigated whether a similar fusion is present in various normal endometrial cell lines. Using reverse transcription PCR, RNase protection and western blotting they showed that the chimeric *JAZF1–JJAZ1* mRNA and protein are found — with identical sequence to that in cancer cells — in endometrial cells but not in other cell types.

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The levels of the chimeric mRNA oscillated with the menstrual cycle in a predictable fashion, implying that the process is regulated rather than accidental. The authors investigated this further by showing that steroid hormones and hypoxia could alter levels of the chimeric mRNA, and that these treatments did not affect the expression of the separate *JAZF1* and *JJAZ1* mRNAs.

So, are chromosomal fusions responsible for these chimeric mRNAs? Southern blotting and fluorescence *in situ* hybridization showed no evidence of any gene fusion at the DNA level, leading the authors to investigate *trans*-splicing of the individual mRNAs. When an extract from endometrial cells that can mediate splicing *in vitro* was mixed with purified RNA from rhesus fibroblast cells, chimeric products were found containing rhesus and human sequences, showing that the mRNAs had been spliced together rather than arising either from rearrangements in DNA or from the polymerase switching templates during transcription.

The next step will be to discover the mechanism by which two separate mRNAs are selected for splicing together. It is intriguing that gene fusions in cancer cells have recapitulated the normal synthesis of chimeric products that in normal cells is mediated at the mRNA level. It will be interesting to see whether co-localization of the genes during transcription, which is possibly required for *trans*-splicing to occur, predisposes towards the gene fusion or whether it is merely that the growth advantages of this fusion are selected for when, by chance, they occur in cancer cells.

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ORIGINAL RESEARCH PAPER Li, H., Wang, J., Mor, G. & Sklar, J. A neoplastic gene fusion mimics *trans*-splicing of RNAs in normal human cells. *Science* **321**, 1357–1361 (2008)
FURTHER READING Kapranov, P., Willingham A. T. & Gingeras, T. R. Genome-wide transcription and the implications for genomic organization. *Nature Rev. Genet.* **8**, 413–423 (2007)