GENE REGULATION

RNA-mediated inheritance spotted in mice

A study of spotted mice suggests that as well as contributing their usual cargoes of DNA, mammalian sperm and eggs might also transmit heritable genetic information in the form of RNA.

Mendel's laws of inheritance have had their fair share of challenges. Paramutation, which was described 50 years ago, is one well-known violation: in this case, an allele interacts with its homologue and somehow causes in it a heritable epigenetic change. There is now evidence that one instance of this phenomenon in mice is mediated by RNA: the authors propose that a mutant RNA transcript alters the expression of

the wild-type allele and transmits the modified phenotype to future generations of offspring.

The study, by Minoo Rassoulzadegan and colleagues, was carried out on the mouse *Kit* gene, which when mutated causes spots of white fur to appear on otherwise dark-coloured mice. The null allele of *Kit* that gives this phenotype (*Kit^{tm1Alf}*) is dominant; however, most offspring of a *Kit* heterozygous mouse and a wild-type one had white spots, even when they carried two copies of the wild-type *Kit* allele.

The explanation for this illegitimate inheritance pattern was suggested by the fact that the wild-type *Kit* allele produces many oddly sized RNA transcripts. Could the allelic interaction somehow involve RNA? Indeed, when RNA from *Kit* mutant cells was injected into wild-type fertilized eggs, mice developed white spots.

Although the precise molecular details are not known, the fact that aberrantly sized RNA transcripts accumulate in the sperm of mutant mice lends plausibility to the model whereby RNA is passed using the sperm to offspring, where it would

alter gene expression in the absence of the mutant DNA copy. The involvement of small interfering RNAs or microRNAs in all this seems likely given their recognized association with paramutation and other epigenetic phenomena: the regulatory RNAs might degrade the normal *Kit* message, or modify the wild-type *Kit* allele itself.

The fitness benefits of an RNA-based inheritance system are easy to imagine: as the authors speculate, any advantage that a mutated allele conferred in one generation could be passed on to offspring, without the need to rely on mutation and selection to increase the representation of the fitter allele. After many years of living in the shadows, RNA is being revealed as an inheritance molecule in its own right.

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ORIGINAL RESEARCH PAPER

Rassoulzadegan, M. *et al.* RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. *Nature* **441**, 469–474 (2006)

FURTHER READING Chandler, V. L. & Stam, M. Chromatin conversations: mechanisms and implications of paramutation. *Nature Rev. Genet.* **5**, 532–544 (2004) | Krawetz, S. A. Paternal contribution: new insights and future challenges. *Nature Rev. Genet.* **6**, 633–642 (2005)