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MICRORNA

Introducing the mirtron

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URLs
Argonaute-1
http://www.expasy.org/uniprot/Q7KY08

Dicer
http://www.expasy.org/uniprot/Q9VCU9

Drosha
http://www.expasy.org/uniprot/Q7KNF1

Introns are a common source of canonical microRNAs (miRNAs), but new research shows that they can also encode a separate class of miRNA precursors — mirtrons — that are processed by a distinct, Drosha-independent pathway.

Animal miRNAs are processed in two stages: first, a hairpin (pre-miRNA) is cleaved from a longer transcript (pri-miRNA) by Drosha; second, this hairpin is exported to the cytoplasm and cleaved into two by Dicer to produce the functional miRNA. The Bartel and Lai laboratories now describe how *Drosophila melanogaster* introns can be processed initially by the intron pathway before being cleaved by Dicer into functional miRNAs.

Bartel and colleagues identified 14 *D. melanogaster* introns with the sequence and predicted secondary structure of pre-miRNAs but none of the extended structure and sequence of pri-miRNAs. Lai and colleagues detected expression of the processed versions of these introns in various tissues and developmental stages, and both groups then demonstrated that the products of mirtrons could repress reporter constructs.

To demonstrate that mirtrons depend on splicing and not Drosha, both groups looked at *cis* and *trans* factors. First, they showed that mutation of the nucleotides that are required for splicing abolished production of the mirtrons. Second, they knocked down expression of the lariat debranching enzyme, which resolves spliced introns into a form that can then form hairpins, and found reduced amounts of mirtrons but not of canonical miRNAs. Conversely, knocking down Drosha affected canonical miRNAs but not mirtrons.

In contrast to these differences at the first stage of processing, mirtrons and miRNAs depend on similar *trans* factors at the second stage of processing. Lai and colleagues showed that both depend on Exportin-5 for transfer to the cytoplasm and Argonaute-1 in order to regulate mRNAs, and both groups showed that mirtrons require Dicer for processing the pre-miRNAs into mature products.

The prevalence of mirtrons in other species remains to be seen — it might be that they are more common in species such as flies and nematodes, in which average intron length is close to that of a pre-miRNA, than they are in mammals. Indeed, the Bartel laboratory identified several mirtrons in *Caenorhabditis elegans*. It will also be interesting to better understand their evolutionary dynamics — a proportion of introns might be processed as mirtrons simply because the processing machinery is there. If so, mirtrons would be lost rapidly through selection if they were deleterious, or slowly through genetic drift if they were neutral, and would be retained only if they were beneficial. An important next step will be to catalogue such random or accidental mirtrons as well as the putatively functional ones that have been classified so far.

Patrick Goymer, Associate Editor,
Nature Reviews Genetics

ORIGINAL RESEARCH PAPERS Ruby, J. G., Jan, C. H. & Bartel, D. P. Intronic microRNA precursors that bypass Drosha processing. *Nature* 24 June 2007 (doi:10.1038/nature05983) | Okamura, K. *et al.* The mirtron pathway generates microRNA-class regulatory RNAs in *Drosophila*. *Cell* 28 June 2007 (doi:10.1016/j.cell.2007.06.028)
FURTHER READING Kim, V. N. MicroRNA biogenesis: coordinated cropping and dicing. *Nature Rev. Mol. Cell Biol.* **6**, 376-385 (2005)