RNA WORLD

Back and forth for microRNA regulation

Three new studies have revealed that sense and antisense microRNAs (miRNAs) can be generated by transcription of the same hairpin locus in opposite directions, indicating an even greater functional diversity for these molecules than was already appreciated.

In the fruitfly, the *iab-4* locus encodes a miRNA (*miR-iab-4*) that has been reported to have regulatory effects on neighbouring homeobox (Hox) genes. For example, previous studies have indicated that this miRNA directly represses the Hox gene *Ultrabithorax* (*Ubx*). The three new studies — which used various combinations of bioinformatic, molecular and genetic methods — concluded that a second novel miRNA is produced by antisense transcription of *iab-4*. During embryonic development at least, the two are expressed in non-overlapping spatial domains.

Stark and colleagues, and Tyler and colleagues showed that — like *miR-iab-4* — the antisense miRNA (which is known as *miR-iab4AS* or *miR-iab-8*) has highly conserved, functional target sites in neighbouring Hox genes. Furthermore, ectopic expression of the antisense miRNA caused dramatic developmental defects that were consistent with the deregulation of Hox targets. Evidence for endogenous requirements of the two miRNAs came from a study by Bender. He used genetics to show that loss of expression of *miR-iab4AS*/*miR-iab-8* causes sterility, and that both miRNAs are needed for the normal expression of *Ubx*, although the resulting changes in developmental phenotypes are subtle.

The identification of these sense and antisense miRNA components adds new complexity to the famously complex Hox regulatory network, the precise control of which is required for normal animal development. These studies also raise some intriguing, although unconfirmed, possibilities relating to how such pairs of miRNAs might be involved in producing tightly regulated patterns of gene expression. For example, Stark and colleagues raise the possibility that encoding miRNAs on opposite strands of the same locus provides potential mechanisms for generating tightly regulated, non-overlapping domains of miRNA expression, as is seen for *miR-iab4* and *miR-iab4AS*/*miR-iab-8*. Whether or not this is correct, the fact that the two members of such pairs can have overlapping but distinct targets provides the scope for intricate regulatory relationships between miRNAs and the genes whose expression they modulate.

Two of the studies (Stark *et al.* and Tyler *et al.*) went on to suggest that this phenomenon is not restricted to Hox loci — they identified many more potential and confirmed sense–antisense miRNA pairs in both flies and mammals. Addressing their biological roles will be an important step towards a full understanding of the complexity of gene regulation by miRNAs.

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ORIGINAL RESEARCH PAPERS Stark, A. *et al.* A single Hox locus in *Drosophila* produces functional microRNAs from opposite DNA strands. *Genes Dev.* **22**, 8–13 (2008) | Bender, W. MicroRNAs in the *Drosophila* bithorax complex. *Genes Dev.* **22**, 14–19 (2008) | Tyler, D. M. *et al.* Functionally distinct regulatory RNAs generated by bidirectional transcription and processing of microRNA loci. *Genes Dev.* **22**, 26–36 (2008)

WEB SITES

Manolis Kellis's website:
http://www.csail.mit.edu/biographies/PI/bioprint.php?PeopleID=900034

Welcome Bender's laboratory:
http://bender.med.harvard.edu

Eric Lai's laboratory:
http://www.mskcc.org/mskcc/html/52949.cfm