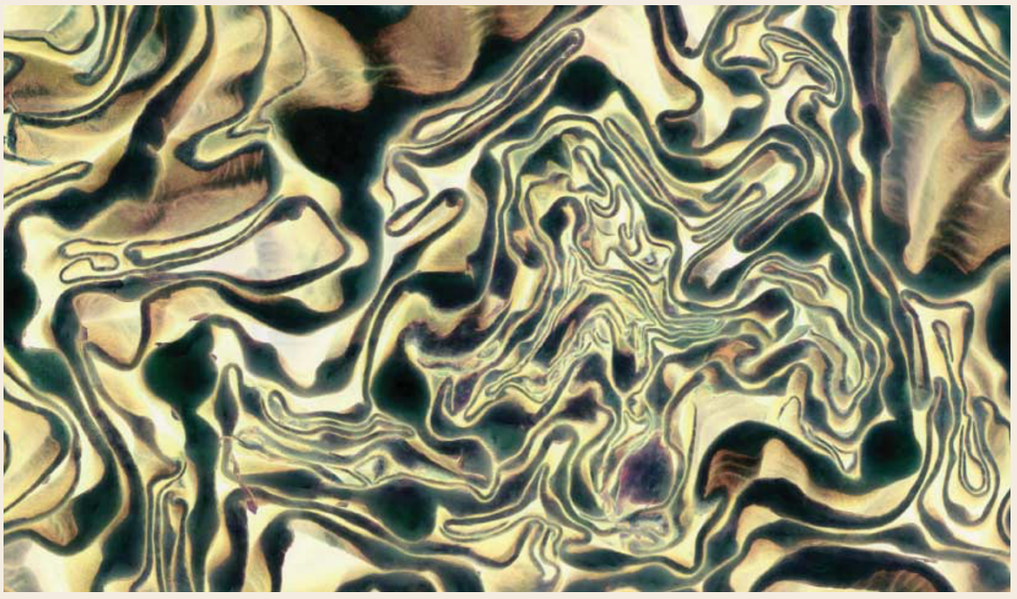
IN THE NEWS



DEVELOPMENTAL GENETICS

Interfering with development

Adding to the growing evidence for the biological significance of RNA interference (RNAi), two recent reports in *Nature Genetics* show that Dicer, an enzyme that cleaves longer RNAs to produce microRNAs and small interfering RNAs (siRNAs), has an essential function in development. Ronald Plasterk and colleagues, and Gregory Hannon and colleagues, show that knocking out Dicer in zebrafish and mice results in early embryonic arrest.

When RNAi was first discovered, most thought that its main purpose was to act as a defence against viruses and transposition. However, increasing numbers of studies are showing that components of the RNAi machinery are involved in essential cell functions.

Using an *in vivo* recombination strategy, Hannon and colleagues targeted Dicer's first RNase III catalytic domain to render the enzyme inactive in mice. Indeed, the authors found that an equivalent mutant form of human DICER1 was unable to cleave siRNA precursors in tissue culture. The development of *Dicer1*$^{-/-}$ mice was arrested by the E7.5 stage. The absence of brachyury expression — a marker of the primitive streak — in *Dicer1*$^{-/-}$ embryos indicates that the mutants arrest before the body plan is laid down during gastrulation.

Components of the RNAi machinery have been implicated in the maintenance of pluripotency in plant and invertebrate development. The fact that, despite many attempts, these authors failed to isolate *Dicer1*$^{-/-}$ embryonic stem (ES) cells indicated that Dicer might be essential for stem cell maintenance. They used Oct4 — a regulator of ES cell maintenance and proliferation — as a marker to look for stem cells in *Dicer1*$^{-/-}$ mice. So, the drastic reduction in *Oct4* expression in these embryos indicated that they had lost stem cells, and points to a potential cause of their lethality owing to stem cell depletion. Whether Oct4 is a direct target of Dicer1 remains to be seen.

Developmental effects of Dicer might be mediated by microRNAs (miRNA) — it has recently been reported that there might be stem cell-specific microRNAs in the mouse. Technical difficulties prevented the authors from testing whether miRNA levels declined in *Dicer1*$^{-/-}$ embryos. Nonetheless, that is exactly what Plasterk and colleagues observed in zebrafish in which *dicer1* had been knocked out.

Mutant *dicer1* zebrafish embryos become sluggish and growth begins to arrest at 8 days post fertilization (dpf), and by 15 dpf all embryos die. The effects are seen earlier in development when *dicer1* is knocked down using morpholinos, probably because the maternal contribution is also knocked down in this case. Using Northern blot analysis, the authors showed that miRNAs build up during the first days of development, and although they persist in wild type and heterozygous fish, they decline in the homozygous mutants.

The role of Dicer in development has now been established beyond any doubt, and it is probably mediated through miRNAs. The challenge will be to identify the relevant miRNA species and ascribe individual functions to them.

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References and links

ORIGINAL RESEARCH PAPERS Wienholds, E. *et al.* The microRNA-producing enzyme Dicer1 is essential for zebrafish development. *Nature Genet.* 5 October 2003 (10.1038/ng1253) | Bernsten, E. *et al.* Dicer is essential for mouse development. *Nature Genet.* 5 October 2003 (10.1038/ng1251)

FURTHER READING Hannon, G. J. RNA interference. *Nature* **418**, 244–251 (2002) | Houbaviy, H. B. *et al.* Embryonic stem cell-specific microRNAs. *Dev. Cell* **5**, 351–358 (2003)