STEM CELLS

Small RNAs cross the divide

One of the properties that make stem cells special is their ability to ignore signals that tell surrounding cells to stop dividing. Previously, how they do this has been something of a mystery, but two new studies now reveal that small RNAs hold the key.

Zamore and colleagues uncovered this role for small RNAs after identifying a new component of the miRNA processing machinery in *Drosophila melanogaster*. They showed that the dsRNA-binding protein Loquacious (LOQS) is essential for the processing of miRNA precursors by the Dicer 1 (DCR1) endonuclease and for the function of small interfering RNAs that silence repetitive regions. Intriguingly, *loqs* mutant female flies are sterile and have small ovaries.

Mutations that block the division or maintenance of germline stem cells (GSCs) are known to give rise to similar phenotypes, as they block the formation of egg chambers (which produce oocytes) by GSCs. The authors found that although GSCs were absent from *loqs* mutant females at 3–4 days of age, some oocytes were produced, so GSCs must have been present initially. Zamore and colleagues concluded that lack of LOQS function, and therefore small RNA production, leads to loss of GSCs due to either death or a failure to divide and produce daughter cells.

In the second study, Ruohola-Baker and colleagues showed that small RNAs have a role specifically in GSC division. They generated

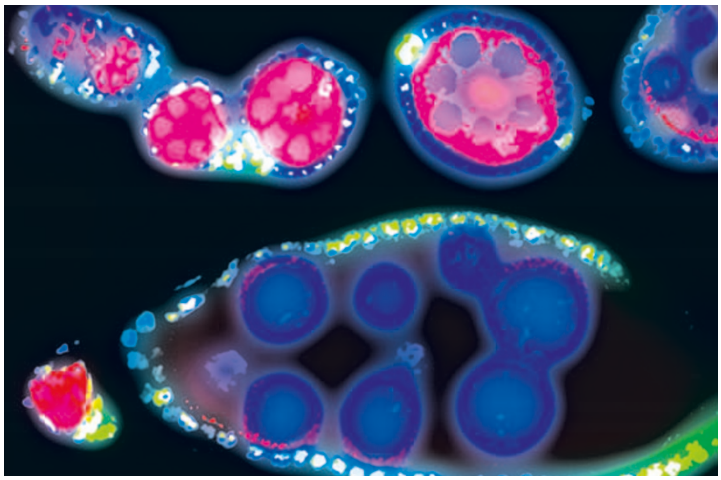

Image courtesy of Hannele Ruohola-Baker, University of Washington, Seattle

flies with ovaries containing GSC clones that were mutant for *dcr1*, and therefore completely lacked miRNAs. The number of GSCs was not altered, indicating that GSC maintenance is not impaired. However, the ovaries contained fewer developing egg chambers, which again indicated a defect in the ability of GSCs to give rise to these structures. In particular, the numbers of GSCs in S, G2 and M phase were reduced, indicating that these cells are blocked in G1 phase.

This study also showed that miRNAs normally allow GSCs to escape cell-cycle arrest by blocking the expression of Dacapo (DAP), a cell-cycle inhibitor. A *dcr1* mutation increased the number of DAP-positive GSCs, and *Dap* overexpression produced a *dcr1*-like phenotype. Furthermore, reducing DAP levels rescued the defects in *dcr1* mutants.

These studies show an essential role of small RNAs in *Drosophila* GSCs, enabling these cells to escape the controls on division that other cells obey. An important aim now will be to determine whether this function of small RNAs is conserved in mammalian stem cells.

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References and links

ORIGINAL RESEARCH PAPERS
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FURTHER READING He, L. & Hannon, G. J. MicroRNAs: small RNAs with a big role in gene regulation. *Nature Rev. Genet.* **5**, 522–531 (2004)
WEB SITES
Hannele Ruohola-Baker's laboratory: http://depts.washington.edu/taneli
Phillip Zamore's laboratory: http://www.umassmed.edu/bmp/faculty/zamore.cfm?start=Research&