SMALL RNAS

Size control

How body size is determined is unclear, but recent evidence suggests that insulin signalling might modulate it by promoting cell growth and proliferation. Hyun *et al.* now report that the microRNA (miRNA) miR-8 positively regulates *Drosophila melanogaster* body size by reducing the expression of the gene encoding U-shaped (USH) — a protein that turns out to inhibit insulin signalling.

The authors previously observed that the human miR-200 miRNA family promotes cell growth. To further study the biological function of miR-200 they analyzed flies deficient in miR-8 — the only *D. melanogaster* homologue of the miR-200 family. miR-8-null flies are much smaller in size and mass than wild-type flies. This phenotype is rescued by expressing miR-8 (or a human miR-200 family member) in the fat body (the fly counterpart of liver and adipose tissue) of these flies, suggesting that these miRNA homologues, and the fat body, modulate fly size.

How do miR-8 and miR-200 regulate body growth? Starting with the premise that important targets should be conserved, the authors compared potential mRNA targets of miR-8 in the fly and those of miR-200 in humans. Of those identified, they validated *USH* and its human homologue, friend of GATA2 (*FOG2*; also known as *ZFPM2*), as targets of miR-8 and miR-200, respectively. Importantly, USH levels are increased in the fat body of miR-8-null fly larvae, and small interfering RNA against *USH* rescues the small body phenotype, suggesting that miR-8 positively regulates body size by downregulating *USH*.

But how do USH and FOG2 inhibit body growth? Insulin signalling, which triggers the sequential activation of phosphoinositide 3-kinase (PI3K) and AKT (also known as PKB) to promote cell growth and survival, is downregulated in miR-8-null and USH-overexpressing fat body cells, which are smaller than their wild-type counterparts. Furthermore, in human cells, overexpression of miR-200 increases cell viability by downregulating *FOG2*. Finally, the authors reveal that FOG2 inhibits insulin signalling by directly binding to the regulatory subunit of PI3K to abrogate its activity.

In short, this study identifies miR-8 and miR-200, and USH and FOG2, as regulators of insulin signalling, which modulate body size by affecting PI3K activity.

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ORIGINAL RESEARCH PAPER Hyun, S. *et al.* Conserved microRNA miR-8/miR-200 and its target USH/FOG2 control growth by regulating PI3K. *Cell* **139**, 1096–1108 (2009)

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