URLs

CELL SIGNALLING

Divided divisions

The activation of heterotrimeric G-protein signalling is essential during asymmetric cell division because this signalling is required for correct spindle position and/or orientation. An important component of this cascade, RIC-8 has been studied in *Caenorhabditis elegans* and mammals. Using *Drosophila melanogaster,* three reports now show that RIC-8 is essential for plasma-membrane localization of G-protein subunits and provide further insights into the RIC-8-mediated regulation of heterotrimeric G-protein signalling.

Heterotrimeric G proteins are composed of non-identical α, β and γ subunits. In most cases, when a Gα subunit binds GDP, it forms a complex with a Gβ and a Gγ subunit, and it functionally dissociates from the Gβγ complex when it binds GTP. The pathway is activated by two types of Gα-binding proteins, GDP-dissociation inhibitors (GDI) and RIC-8, which is thought to be a non-receptor guanine nucleotide-exchange factor (GEF) for Gα.

After studies in *C. elegans* and mammals, three different groups set out to find the role of RIC-8 in *D. melanogaster*. Wang *et al.* and Hampoelz *et al.* both investigated the role of RIC-8 in the asymmetric division of the neuroblast, whereas David and colleagues studied RIC-8 in sensory-organ precursor cells. All three groups show that *ric-8* mutants have several defects — asymmetric localization of cell-fate determinants is not maintained, mitotic spindles are misorientated and the sizes of the two daughter cells become almost equal. These observations indicate that RIC-8 is essential for proper spindle orientation and for controlling daughter-cell size. RIC-8 was also found to be important for gastrulation, a process that is known to rely on G-protein signalling and requires the highly coordinated movement of cells.

In the absence of RIC-8, the G-protein subunits, $G\alpha_i$ and $G\beta_{13F}$, seem to be cytoplasmic, which makes *ric-8* mutants an attractive model in which to study the regulation of heterotrimeric G-protein signalling during asymmetric cell division. Hampoelz and colleagues found that the *ric-8* mutant phenotype resembled *Gβ* but was different from the one described for *Gα* mutants. By contrast, Wang *et al.* showed that both the *ric-8* mutant and the *ric-8 Gβ* double mutant exhibited similar phenotypes to *Gα* mutants in terms of their daughter-cell size phenotype, and concluded that Gα–GDI functions downstream of Gβγ. Even more intriguing, Hampoelz and colleagues also showed that RIC-8 does not function as a GEF for Gα, and that RIC-8 binds both the GDP and GTP forms of Gα — a result that contradicts previous data from *C. elegans*. Whether the observed differences reveal a new function for RIC-8, or whether they are due to mutant variations or limitations of the experimental approaches, remains to be seen.

However, these studies represent important steps in understanding how asymmetric cell division is regulated in *D. melanogaster*, as they all indicate that RIC-8 is required for plasma-membrane localization of G proteins — a much more general role for this protein compared to that originally proposed in *C. elegans*. Although these findings will not end the debate, they are important pieces in the complicated puzzle of spindle position and orientation.

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References and links

ORIGINAL RESEARCH PAPERS David, N.B. *et al. Drosophila* Ric-8 regulates Gαi cortical localization to promote Gαi-dependent planar orientation of the mitotic spindle during asymmetric cell division. *Nature Cell Biol.* **7**, 1083–1090 (2005) | Wang, H. *et al.* Ric-8 controls *Drosophila* neural progenitor asymmetric division by regulating heterotrimeric G proteins. *Nature Cell Biol.* **7**, 1091–1098 (2005) | Hampoelz, B. *et al. Drosophila* Ric-8 is essential for plasma-membrane localization of heterotrimeric G proteins. *Nature Cell Biol.* **7**, 1099–1105 (2005)