HIGHLIGHTS

DEVELOPMENT

Jelly belly shapes up

During organogenesis, inductive signals by several well-characterized signalling molecules, such as Hedgehog and Wingless, generate clusters of visceral-mesoderm precursors. The secreted protein Jelly belly (Jeb) is essential for visceral-mesoderm development during *Drosophila melanogaster* embryogenesis. It is taken up by visceral-mesoderm precursors, but the consequential signalling events during muscle development have not been defined. Now, though, two papers in *Nature* — by Lee *et al.* and Englund *et al.* — report the identification of a receptor and a signalling pathway downstream of Jeb.

Visceral-mesoderm precursors comprise muscle founders and fusion-competent myoblasts. Founder cells, which recruit fusion-competent myoblasts, express the myoblast fusion gene *dumbfounded* (*duf*) and the T-box gene *org-1*; and fusion-competent cells express another fusion gene, *Sticks and stones* (*sns*). Lee *et al.* showed that overexpressing Jeb activates *duf* and *org-1*, and downregulates *sns,* which indicates a potential role for Jeb in specifying founder cells. In *jeb*-mutant embryos, no visceral founders were specified.

Because the extracellular signal-regulated protein kinase/mitogen-activated protein kinase (ERK/MAPK) pathway is required in the somatic-muscle lineage for specifying founder cells, Lee *et al.* investigated this signalling pathway in the visceral mesoderm. Both Lee *et al.* and Englund *et al.* found ERK/MAPK to be activated in visceral-mesoderm precursors. Indeed, activated ERK/MAPK was absent in *jeb* mutants. On this basis, activation of ERK/MAPK should rescue *jeb* mutants — which it did.

So how does Jeb signal to ERK/MAPK? The receptor tyrosine kinase Alk was expressed in the early visceral mesoderm in cells directly adjacent to somatic mesoderm cells that were expressing jeb. Furthermore, activated ERK/MAPK was detected in cells that expressed Alk and that had taken up Jeb. These observations hinted that Alk was the Jeb receptor. Both groups saw that, in the absence of *Alk*, embryos resembled *jeb*-mutant embryos. Furthermore, ectopic expression of Alk — in particular, using a constitutively active version that resembles the human *ALK* oncogene (which contributes to non-Hodgkin's lymphoma) — rescued the phenotype of *jeb* mutants. Both groups then showed that, in the absence of Alk activity and in *jeb*-mutant embryos, *duf* was no longer expressed in muscle-founder cells.

Englund *et al.* reported that Jeb and Alk co-immunoprecipitated, and that this was dependent on the extracellular domain of Alk. Further biochemical assays by both groups confirmed a high-affinity Alk–Jeb interaction. Englund *et al.* also found that, although the kinase activity of Alk wasn't required for Jeb binding, it was required for Jeb to be taken into the visceral-mesoderm cells and for Jeb's subsequent degradation — point mutations in the catalytic domain prevented Jeb uptake.

Alk therefore seems to be the receptor — or part of a receptor complex — that binds Jeb and subsequently signals through ERK/MAPK to specify visceral-mesoderm founder-cell fate. So Jelly-belly signalling seems to be taking shape.

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Jeb: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0033681
Duf: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0028369
Org-1: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0021767&resultlist=fbgn3575.data[0]
Sns: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0024189
ERK/MAPK: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0003256
Alk: http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0040505&resultlist=fbgn4214.data[0]

References and links

ORIGINAL RESEARCH PAPERS Lee, H.-H. *et al.* Jelly belly protein activates the receptor tyrosine kinase Alk to specify visceral muscle precursors. *Nature* **425**, 507–512 (2003) | Englund, C. *et al.* Jeb signals through the Alk receptor tyrosine kinase to drive visceral muscle fusion. *Nature* **425**, 512–516 (2003)

WEB SITES

Manfred Frasch's laboratory: http://adsr13.mssm.edu/domains/dept/facultyInfo.epl?objname=biomol&user=frascm01&sid=20437_1

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