Braking proliferation

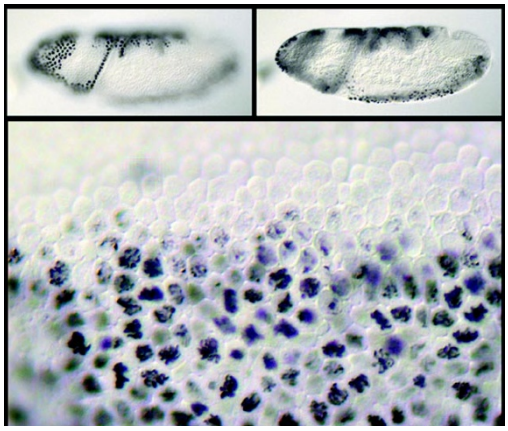
During the development of any organism, it is essential that cell proliferation and morphogenesis are strictly controlled. Without these controls, the development of an organism can be seriously affected, as can processes such as gastrulation and mesoderm invagination.

Three recent papers — Seher and Leptin (*Curr. Biol.* **10,** 623–629, 2000), Mata *et al.* (*Cell* **101,** 511–522, 2000), and Groβhans and Wieschaus (*Cell* **101,** 523–531, 2000) — have now addressed the fundamental problem of balancing cell growth with morphogenesis, using the mesoderm and germline of *Drosophila melanogaster*. During stage 14 of *Drosophila* embryonic development, mitotic domains are marked by the Cdc25 homologue String. Removal of String from most of these domains has no effect on the developing embryo, except in mitotic domain 10, where there is usually a gap between the initiation of String expression and the onset of mitosis. During this gap the cells in domain 10 elongate and invaginate into the embryo, forming the mesoderm. As there is no cell division during this crucial morphogenetic movement, it has been proposed that a proliferation brake must act on String.

Seher and Leptin carried out a genetic screen to look for this proliferation brake, and identified a new putative serine/threonine kinase, termed Tribbles (after the multiplying Tribbles in Star Trek). In a concurrent screen by Groβhans and Wieschaus, *tribbles* was also identified as a mitotic block, as was as the new gene named *Frühstart*. Both groups observed that *tribbles* mutants lose the gap between String expression and mitosis, and hence the block on proliferation before invagination (picture shows the gastrulation defects exhibited by *tribbles*-mutant embryos).

Together, these findings hinted that Tribbles may act as a proliferation brake through downregulation of String (embryos lacking both String and Tribbles have a wild-type phenotype). However, the precise mechanism of action was unknown, as a kinase-dead Tribbles could still block proliferation.

Mata *et al.* have also identified Tribbles, but this time as a regulator of germ-cell development. During germline development a complicated set of cell divisions occurs to generate a 16-cell cystocyte, which goes on to form the 15 nurse cells and single oocyte of the developing egg chamber. Overexpression of String leads to fewer cystocyte divisions, whereas overexpression of Tribbles generates egg chambers with more than 15 nurse cells and sometimes more than a single oocyte. As the cell-cycle controls involved in germline cystocyte development are not well understood, Mata *et al* went on to investigate the function of Tribbles during development of the wing disc. Here, overexpression of Tribbles generates wings that contain a smaller number of cells that are larger than those of the wild type (giving a wing of the correct size). Overexpression of String rescues this phenotype. Using this *in vitro* system they determined that Tribbles directly and post-translationally degrades String through the proteasome, a finding they went on to verify in the embryo.



Together, the three studies seem to show that Tribbles causes the degradation of String. Braking cell proliferation in this manner would ensure that complex morphogenetic processes could be completed without the added complications of cell division. As Seher and Leptin have also identified other genes in their screen that could be proliferation brakes, and as Groβhans and Wieschaus have identified *Frühstart*, it could be that Tribbles acts in conjunction with these genes to cause String degradation or to elicit proliferation braking at different stages of development. The identification and clarification of these genes will be an exciting development in the mitotic brake story.

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