DEVELOPMENT

Remembering Hedgehog

A study into the patterning of the fruitfly wing has led to a new model of how morphogen gradients confer positional information. It concludes that the response of cells to Hedgehog (HH) depends not so much on the local concentration of HH but on their past history of exposure to this morphogen.

In the classic morphogen model, cells develop distinct expression patterns according to their position in a morphogen gradient. In the wing imaginal disc, HH is expressed only in the posterior compartment; from there it diffuses for 10–15 cells into the anterior compartment, in which it leads to at least three distinct domains of target gene expression. However, a direct link between HH concentration and a gene-expression pattern has not been found. To investigate this relationship, the authors devised a mathematical model of HH signalling — based on the known HH-signalling network — and then tested its predictions *in vivo*.

The model suggested that, at steady state, the HH gradient has only one concentration threshold — it behaves like a switch — and therefore cannot specify multiple

expression domains. To reconcile these observations, the authors modelled the dynamic establishment of the HH gradient: this showed that the expression of HH extends for a brief period beyond its steady-state anterior boundary, and that this ‘overshoot’ eventually recedes due to the HH-induced expression of Patched (PTC), an HH-sequestering molecule. By the time the system returns to the steady state, there are three cell states: cells that have never seen HH, those that have only seen it transiently (those in the overshoot domain) and those that have seen it constantly.

These predictions were confirmed experimentally: an *hh* temperature-sensitive mutant that was returned to the permissive temperature did indeed show a transient overshoot, which was followed by an HH-induced rise in PTC expression and then a posterior refinement. The existence of the three cell states was supported by the finding that cells that experience transient exposure to HH maintain the expression of *decapentaplegic* (*dpp*) but not of *ptc* or *collier* (also known as *knot*), and that the expression boundaries of

the HH-target genes *dpp* and *collier* overlap when the overshoot domain is prevented from forming.

This work provides a new framework for interpreting morphogen patterning in the many tissues and organisms in which HH signalling is conserved. It also highlights the need to consider temporal dynamics in studies of developmental processes.

Tanita Casci

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