ORGANOGENESIS

A mean spleen gene

The identification of a gene required for the development of a specific vertebrate organ is a big event in developmental biology. With a new mouse knockout, Lu *et al.* have shown that the gene *capsulin* is necessary for spleen development.

Capsulin is a basic helix–loop–helix (bHLH) transcription factor expressed in mesenchymal cells during the early development of the heart, gut, kidneys and lungs. In the *capsulin* mutants made by Lu *et al.*, the initial stages of spleen development seem normal but the subsequent expansion of splenic precursor cells does not occur. And the end result? No spleen.

Two other genes, *Hox11* and *Bapx1*, have a similar expression pattern and a similar knockout phenotype to *capsulin*. Both genes encode homeobox transcription factors. Lu *et al*. conclude that *capsulin*, *Hox11* and *Bapx1* may work together within the mesenchyme to regulate epithelial–mesenchymal interactions during the early development of the spleen. They also point out that cooperation between bHLH and homeobox proteins has been reported in pituitary development, and may represent a common developmental mechanism.

Knockouts in *capsulin* also have severe defects in the lung and the kidney — although the homozygotes survive to term, they die within minutes of birth because of breathing problems. This phenotype was reported last year in an independent *capsulin* mouse knockout made by Quaggin *et al.*, who also noted defects in branching morphogenesis in lung and kidney. So although the most severe organ defect in the *capsulin* mutant is the absent spleen, further analysis of capsulin and its cooperation with other transcription factors will have wide-ranging relevance to organogenesis in vertebrates.

Mark Patterson

References and links

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DEVELOPMENTAL BIOLOGY

New balancing tricks

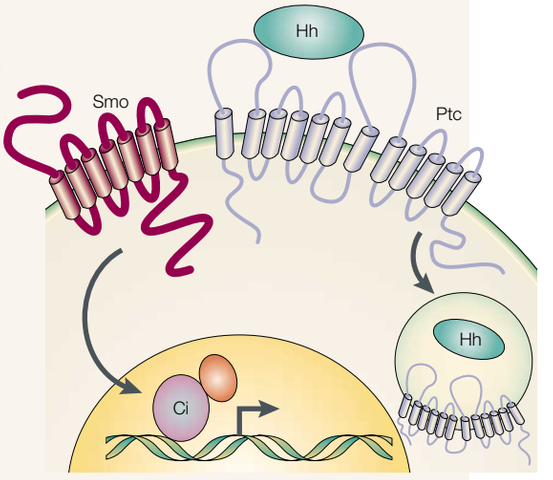
The secreted signalling molecule Hedgehog (Hh) was so baptized in *Drosophila* because of the effects of its mutation, which turns the ventral surface of the embryo into a lawn of spiky denticles. Hh was subsequently found to belong to a conserved family of secreted signalling molecules, required for growth and patterning during animal development. Cellular responses to Hh are controlled by two transmembrane molecules: Patched (Ptc), a multi-pass membrane protein that binds Hh; and Smoothened (Smo), a seven-pass protein that relays the signal to nuclear effectors. When Hh is not around, Ptc prevents constitutive signalling by Smo — a repression that is relieved when Hh binds to Ptc.

Two recent papers in *Cell* and *Molecular Cell* report a new mechanism whereby these proteins regulate the activity of one another post-translationally.

All cells known to respond to the Hh signal express high levels of Smo. Together, both papers show that Ptc causes the levels of Smo protein to go down, unless Hh is present to make them go up. Both effects happen after Smo is transcribed, because Smo transgenes are regulated in the same way as the endogenous gene and Smo regulation is independent of *cubitus interruptus* (*ci*), the transcription factor through which the Hh signal is transduced.

What is the post-transcriptional change and how does it affect Smo? *Drosophila* cells in culture that have been bathed in Hh accumulate a slower migrating, phosphorylated form of Smo — an effect that is mimicked by removing Ptc. Interestingly, as the proportion of phosphorylated Smo rises, levels of Ptc protein begin to drop.

Previous experiments on mammalian homologues had indicated that Ptc and Smo exist as a preformed complex at the membrane; and the binding of Hh to Ptc was presumed to cause the conformational change that nudged Smo into signalling mode. Denef *et al.* now offer an alternative view: binding of Hh to Ptc induces the internalization of Ptc through intracellular vesicles (probably doomed for the lysosome), removing it from the cell surface, and causes a concomitant accumulation of active, phosphorylated Smo at the plasma membrane. So it seems that Hh treatment can prevent a Ptc-dependent alteration in the post-translational modification of Smo.



Alcedo *et al.* would agree. They propose a 'self-correcting' model that imposes a strict interdependence between the presence of Hh and the activities of Smo and Ptc. In their view, Hh signalling has two consequences: the stabilization of Smo protein (independently of Ci), and the transcriptional activation of Ptc that, by silencing Smo, makes signalling entirely dependent on the presence of the ligand. The system is self-correcting because any imbalance is readjusted to an equilibrium that resists small perturbations, and in which Ptc inhibits Smo as rapidly as possible when Hh is not there.

Because mutations in both Ptc and Smo have been linked to basal cell carcinoma, unravelling the relationship between these molecules has biological implications that extend beyond development. The careful balance of the activities of Hh, Smo and Ptc is therefore needed both to ensure correct development and to circumvent cancer.

Tanita Casci

References and links

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WEB SITES Stephen Cohen's lab | Markus Noll's homepage at the University of Zurich