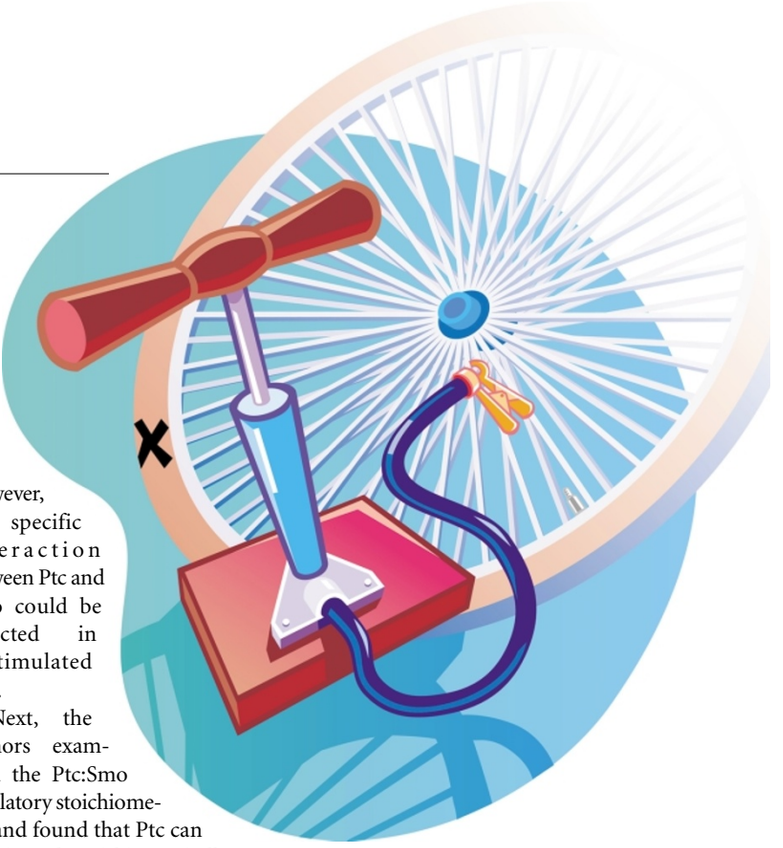
HIGHLIGHTS

SIGNAL TRANSDUCTION

Patched for pumping



The Hedgehog (Hh) pathway is activated by binding of the Hh ligand to the transmembrane protein Patched (Ptc), which relieves the inhibitory effect that Ptc has on another transmembrane protein, Smoothened (Smo). Smo then regulates transcription through the transcription factor Cubitus interruptus. To date, most models have predicted that a direct interaction between Ptc and Smo accounts for this, but evidence from Phil Beachy's lab now points to Ptc being a transmembrane molecular transporter that indirectly inhibits Smo.

Beachy's group began by scrutinizing existing models. In the 'stable heteromeric receptor' model, Ptc and Smo are associated; the binding of Hh to Ptc relieves the suppression of Ptc on Smo but the Ptc–Smo complex doesn't dissociate. Extra Ptc would therefore make no difference to Hh-pathway activity, because this excess would not be complexed with Smo. However, this was found not to be the case — extra Ptc had a marked effect on Hh-pathway activation. Furthermore, a suppressing influence on the pathway of a Hh-insensitive Ptc mutant couldn't be outcompeted by wild-type Ptc. Together, these results rule out this model.

In the 'dissociating heteromeric receptor' model, Ptc and Smo still interact but, when Hh binds to Ptc, it causes the complex to dissociate, thereby generating free, active Smo. However, no specific interaction between Ptc and Smo could be detected in unstimulated cells.

Next, the authors examined the Ptc:Smo regulatory stoichiometry and found that Ptc can function sub-stoichiometrically to suppress Smo, which supports a model in which Ptc regulates Smo catalytically. Having ruled out changes in Smo stability or phosphorylation as possible mechanisms, the authors looked further afield. Ptc is similar to a family of bacterial proton-gradient-driven transmembrane molecular transporters known as RND ('resistance, nodulation and division') proteins. RND proteins and Ptc have a similar 12-membrane-spanning domain structure, and both have a GXXXD motif (mutation of which impairs RND transporter function). Notably, three of six missense mutations in Ptc that are linked to Gorlin's syndrome — a genetic disease that predisposes people to basal-cell carcinoma — affect the conserved glycine or aspartate residues. This is highly indicative of a conserved function between these transmembrane proteins.

In the case of Ptc, exactly what this function is remains unclear. One possibility (by analogy with other systems) is that, in the absence of Hh, Ptc translocates a small molecule that conformationally regulates the active state of the seven-membrane-spanning Smo protein. Such a small molecule could result in the loss of Smo activity or the gain of Smo inhibition. In support of this, small-molecule agonists and antagonists of the Hh pathway seem to bind directly to Smo and to affect its activity. But one step at a time — hedgehogs aren't usually famous for their speed!

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Taipale, J. *et al.* Patched acts catalytically to suppress the activity of Smoothened. *Nature* **418**, 892–897 (2002)
FURTHER READING Ingham, P. W. & McMahon, A. P. Hedgehog signaling in animal development: paradigms and principles. *Genes Dev*. **15**, 3059–3087 (2001)