AXON GUIDANCE

What Sonic did next

The signalling molecule Sonic hedgehog (Shh) has been investigated so extensively over the past few years that it is a wonder that there is anything left to discover about its properties. However, as Charron and colleagues reveal in a report in *Cell*, it still has a few surprises up its sleeve. In addition to its classic role as a morphogen, it can also act as an axon-guidance cue.

In the vertebrate embryo, a group of neurons that originate in the dorsal spinal cord send axonal projections to the ventral midline (or floor plate), where they cross to the other side to generate commissural tracts. Netrin-1 has been identified as an essential chemoattractant that guides these axons towards the ventral midline, but other factors are probably also required.

Shh is expressed in the floor plate of the vertebrate neural tube, and can act at a long range from its source, so it was a potential candidate. Indeed, Charron *et al.* showed that Shh, like Netrin-1, can reorientate commissural axons *in vitro*. They also showed that the growth cones of frog spinal axons changed their course and grew towards a source of Shh, further supporting the idea that Shh acts directly as a chemoattractant.

By blocking the function of the Shh receptor Smoothened (Smo) using the specific inhibitor cyclopamine, the authors also obtained insights into the molecular mechanism that underlies the chemoattractant properties of Shh. They found that, at least *in vitro*, cyclopamine prevented commissural axons from turning towards a source of Shh, but did not affect their response to Netrin-1. To find out whether Shh is required *in vivo* for commissural axon guidance, they selectively disrupted Smo function in commissural axons. Consistent with Shh acting as a midline chemoattractant, this resulted in defects in commissural axon guidance. Importantly, this also implies that the commissural neurons have a cell-autonomous requirement for Shh signalling.

So, Charron *et al.* provide compelling evidence that Shh, acting through Smo, functions as an axon-guidance cue at the floor plate of the developing spinal cord. Unlike Netrin-1, it cannot promote axonal outgrowth, but it seems to be an essential component of the molecular mechanism that mediates attraction of axons to the ventral midline. These findings should stimulate investigations into whether other morphogens can 'double up' as axon-guidance molecules once their patterning work is done.

Heather Wood, Senior Editor,
Nature Reviews Neuroscience

References and links

ORIGINAL RESEARCH PAPER Charron, F. *et al.* The morphogen Sonic hedgehog is an axonal chemoattractant that collaborates with Netrin-1 in midline axon guidance. *Cell* 2003 March 18 (DOI:10.1016/S0092867403001995)

STRUCTURE WATCH

Step on

The molecular motor myosin V moves processively along actin filaments, and several competing models have been proposed to explain this movement. At present, the 'hand-over-hand' model is the most widely accepted and, in this model, the two myosin V head domains spend most of their ATPase cycle attached to actin. A 'step' occurs when the trailing head detaches from actin and is moved forward to become the new leading head. This forward motion is thought to be generated mainly by tilting of the light-chain domain (LCD) that is adjacent to the attached head — that is, the LCD functions as a mechanical lever arm. However, the extent and timing of this motion have remained poorly defined.

Now, though, in *Nature*, Goldman and colleagues report the development of a single-molecule fluorescence polarization technique that has allowed them to determine the orientation of individual LCDs of brain myosin V in real time and in three dimensions. In the presence of ATP, they saw that the LCD tilts between two well-defined angles as myosin V moves processively along actin, and that myosin V takes an ~37-nm step for each change in angle and for each ATP hydrolysed. The data indicate that myosin V steps involve transitions of the head domains between two actin-bound structural states, and support the hand-over-hand model for myosin V movement. In addition, this work has given us a technique that is "…applicable to the study of real-time structural changes in other biological processes".

REFERENCE Forkey, J. N. *et al.* Three-dimensional structural dynamics of myosin V by single-molecule fluorescence polarization. *Nature* **422**, 399–404 (2003)

Show some self-control

The prototype member of the Src family of tyrosine kinases, c-Src, is known to use autoinhibition to control its activity, and assembly of its autoinhibited form is triggered by a phosphotyrosine residue in its carboxy-terminal tail, which binds to its Src-homology-2 (SH2) domain. However, despite this knowledge, the autoinhibitory mechanism of a relative of c-Src — the cellular form of the Abelson leukaemia virus tyrosine kinase (c-Abl) — has remained unclear. The catalytic activity of c-Abl is properly regulated, even though it lacks the above-mentioned phosphotyrosine. So, to provide insights into c-Abl autoinhibition, Superti-Furga, Kuriyan and colleagues now describe in *Cell* crystal structures of autoinhibited fragments of a splice variant of c-Abl that is naturally myristoylated (c-Abl 1b).

The structures showed that the amino-terminal myristoyl moiety of c-Abl 1b binds to its kinase domain, which induces a sharp bend in the carboxy-terminal helix that is at the base of this domain. This conformational change functions as a gating mechanism and allows the SH2 and SH3 domains of c-Abl 1b to dock onto the kinase domain, which results in an autoinhibited state that is remarkably similar to that of c-Src. However, the authors saw significant differences between the conformations of the kinase domains in the autoinhibited forms of c-Abl and c-Src. These differences allowed them to explain the ability of various drugs to inhibit the catalytic activity of c-Abl, but not that of c-Src.

REFERENCE Nagar, B. *et al.* Structural basis for the autoinhibition of c-Abl tyrosine kinase. *Cell* **112**, 859–871 (2003)