

AXON GUIDANCE

What Sonic did next

The signalling molecule Sonic hedgehog (Shh) has been investigated so extensively over the last few years that it is a wonder that there is anything left to discover about its properties. However, as Charron and colleagues show 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. However, it cannot be the only factor that is required, because in *Netrin 1* knockout mice, some of these axons are still attracted towards the floor plate.

As Shh is expressed in the floor plate of the vertebrate neural tube, and can act at a long range from its source, it was considered to be a possible candidate for one of the missing factors. 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 could change their course and grow towards a source of Shh, further supporting the idea that Shh acts directly as a chemoattractant.

By blocking the function of the Shh receptor Smoothed (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.

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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* 18 March 2003 (doi:10.1016/S0092867403001995)



IN BRIEF

SYNAPTIC TRANSMISSION

Control of neurotransmitter release by an internal gel matrix in synaptic vesicles.

Reigada, D. *et al. Proc. Natl Acad. Sci. USA* **100**, 3485–3490 (2003)

In neurotransmitter vesicles from *Torpedo*, 95% of acetylcholine and ATP is found to be adsorbed to an intravesicular proteoglycan matrix, rather than being in free solution. This 'smart gel', which includes the proteoglycan SV2, releases neurotransmitter in response to changes in ion concentration, and could modulate the amount of transmitter released during vesicle fusion.

NEURODEGENERATION

Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in *Drosophila*.

Yang, Y. *et al. Neuron* **37**, 911–924 (2003)

Mutations in the *parkin* gene that abolish the protein's E3 ubiquitin ligase activity are associated with early-onset Parkinson's disease. One substrate of Parkin is Pael-R, and Yang *et al.* show that expression of human PAELR in *Drosophila* causes degeneration of dopamine neurons, and that co-expression of Parkin prevents this degeneration.

CELL BIOLOGY OF THE NEURON

The role of presenilin cofactors in the γ -secretase complex.

Takasugi, N. *et al. Nature* **422**, 438–441 (2003)

Reconstitution of γ -secretase activity.

Edbauer, D. *Nature Cell Biol.* 7 April 2003 (10.1038/ncb960)

These two papers provide new insights into the components of γ -secretase, an unusual protease that is involved in the formation of amyloid- β peptide by cleavage of amyloid precursor protein. Edbauer *et al.* show that γ -secretase activity can be reconstituted in yeast by the co-expression of human presenilin and three putative cofactors — nicastrin, APh1 and PEN2. Takasugi *et al.*, meanwhile, have found evidence that, in *Drosophila*, APh1 stabilises the presenilin holoprotein in the complex formed by the proteins. PEN2 then seems to interact with the APh1–presenilin–nicastrin complex to cause endoproteolysis of presenilin and confer γ -secretase activity on the complex.

DEVELOPMENT

Wnt-mediated axon guidance via the *Drosophila* Derailed receptor.

Yoshikawa, S. *et al. Nature* 16 March 2003 (10.1038/nature01522)

In *Drosophila*, axons that cross the midline during development through the anterior commissure express an atypical tyrosine kinase receptor, Derailed, that prevents them from entering the posterior commissure. Yoshikawa *et al.* show that Derailed mediates this repulsion by acting as a receptor for Wnt5, a secreted signalling molecule, and that Wnt5 is expressed by neurons around the posterior commissure.