observed a decrease in the number of EGF-responsive neural progenitors in the SVZ. A similar result was obtained if an antisense oligonucleotide was used to inhibit sAPP synthesis.

So, these findings indicate that EGF-induced neural precursor proliferation in the adult SVZ is at least partly mediated by the release of sAPP. It remains to be seen whether sAPP has a similar role in the human brain. However, Caillé *et al.* raise the tantalizing possibility that sAPP's role in adult neurogenesis could provide a link between aberrant APP processing and some of the cognitive impairments that are associated with Alzheimer's disease.

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AXON GUIDANCE

Making axons cross

Numerous parallels can be drawn between axon guidance mechanisms in flies and vertebrates, including prominent roles for Slit repellents and the Roundabout (Robo) family of Slit receptors that mediate their repulsive actions. However, although the Slit–Robo interaction is crucial for guiding axons across the CNS midline in *Drosophila melanogaster*, an equivalent mechanism in vertebrates has remained elusive. Two new studies by Marc Tessier-Lavigne and colleagues attempt to rectify this situation, and the authors also uncover a new mechanism involving an unexpected role for a Robo protein as a negative regulator of Slit responsiveness.

In the vertebrate CNS, two populations of interneurons are recognized on the basis of their axonal trajectories — association neurons project ipsilaterally, whereas commissural neurons project contralaterally across the ventral midline. In *D. melanogaster*, Slit repels commissural axons away from the midline after crossing. In rodents, Slit homologues are expressed at the ventral midline, and Robo1 and Robo2 are expressed in commissural axons, but a double knockout of *Slit1* and *Slit2* in the mouse produces no discernable midline crossing defects.

In one of the new studies, Long *et al.* made triple mutants that lacked all three mammalian Slits (Slits 1–3). In these mutants, many commissural axons stalled at the floor plate and failed to cross, indicating that Slits were contributing to the repulsion of axons out of the midline. Robo1 mutants showed a similar phenotype. Intriguingly, although a significant fraction of commissural axons express only Robo2, a Robo2 knockout did not produce crossing defects. To explain this result, the authors suggest that Robo1-expressing axons guide the Robo2-expressing axons across the midline. The authors also provided evidence that a combinatorial code of Robo1 and Robo2 determines how far commissural axons are repelled away from the midline, as in flies.

So, Slit homologues in vertebrates seem to act through Robo receptors to repel commissural axons away from the midline after crossing. But how do the axons suppress their responsiveness to Slit until they reach the midline? In *D. melanogaster*, the Commureless (Comm) protein sequesters Robo1 in intracellular compartments to prevent it from being displayed on the axonal membrane as growth cones approach the midline. No homologue of Comm has been identified in vertebrates, but in an unexpected twist, Sabatier *et al.* showed that the

Robo homologue Rig-1 (also known as Robo3) has an analogous functional role to Comm, but works through a different mechanism. In *Rig-1*-knockout mice, commissural axons were prematurely repelled by Slit, preventing them from reaching and crossing the midline. The levels of Robo1 and Robo2 expression were unaffected, but the authors suggest that Rig-1 could act as a dominant-negative Slit receptor, or that it could affect the signalling pathway downstream of Robo.

It is intriguing that the vertebrate 'anti-Robo' molecule is itself a member of the Robo family. Rig-1 is expressed in a reciprocal pattern to the other Robo proteins, being expressed at a high level before midline crossing and downregulated after crossing, consistent with its role in preventing Slit responsiveness. It would be interesting to find out how these divergent properties arose during evolution. It will also be important to establish whether flies and vertebrates evolved different mechanisms to solve the problem of midline crossing. Robo1 and Robo2 expression is not affected by removal of Rig-1, indicating that a Comm-like mechanism remains to be discovered in vertebrates. So is there also a Rig-1-like mechanism that operates in flies?

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