projections extend[2]. Some guidance cues are produced near the advancing growth cone, are tethered to the surface of nearby cells or to the extracellular environment, and can locally steer growth cones. Other, secreted and diffusible, guidance cues are thought to act over long distances by forming gradients that can either attract (Fig. 1a) or repel extending neuronal projections. But little is known about how these cues are presented to neuronal projections, or how their range of action is regulated during neural development.

Netrins are potent secreted guidance cues[3,4]. In organisms from worms to mammals, Netrins attract axons from specific neuronal populations that cross from one side of the body to the other, towards the midline of the CNS. Long-range attraction by Netrin is mediated by receptors of the Deleted in Colorectal Cancer (DCC) protein family, which includes the *Drosophila* protein Frazzled. Intriguingly, Netrins can repel other populations of neurons that are directed away from the midline. Long-range repulsion by Netrin is mediated by a receptor complex that includes DCC and a member of the UNC-5 family of cell-surface-located receptors[5,6]. Netrin receptors can be found on the surface of the growing axon and, on binding secreted Netrins, they send signals inside the axon to tell it which way to go. But in *Drosophila*, Frazzled is sometimes required not on the growing axons, but rather in their intermediate targets. How might Frazzled be used here?

To tackle this problem, Hiramoto *et al.*[1] looked at the distribution of Netrin in the developing fly nervous system. There are two Netrins in *Drosophila*, Netrin-A and Netrin-B. Both are strongly expressed in the CNS midline, where they work to attract axons[7,8]. Interestingly, Hiramoto *et al.* find that a substantial fraction of Netrin protein also localizes to axons in a dorsolateral CNS region, far from where Netrin is made. This dorsolateral region also contains abundant Frazzled protein; indeed, Frazzled and Netrin are found on the same dorsolateral axons. This localization of Frazzled requires its cytoplasmic domain. A closer look revealed dramatic changes in Netrin distribution either in the absence of Frazzled or following the forced expression of Frazzled in the wrong places. So Frazzled plays a key part in capturing and localizing Netrin protein at specific sites in the fly CNS.

Does this precise Netrin localization serve to guide axons? Hiramoto *et al.* looked at CNS neurons called dMP2 neurons, which are known to require Netrin and Frazzled for guidance, and determined how much these neurons rely on dorsolaterally localized Netrin. In wild-type *Drosophila* embryos, axons from dMP2 neurons first grow laterally away from the midline, then turn posteriorly to grow parallel to the body axis within the CNS (Fig. 1b). Hiramoto *et al.* find that, in embryos lacking Netrin or Frazzled, this characteristic turning behaviour of dMP2 axons is altered: they extend too far laterally and do not turn posteriorly. In embryos lacking Frazzled, this altered behaviour can be corrected by selectively expressing Frazzled in lateral neurons, but not in dMP2 neurons themselves, consistent with the observation that dMP2 neurons do not express Frazzled. Experiments using altered Frazzled proteins show that the ability of Frazzled to guide dMP2 axons and localize Netrin does not require Frazzled's cytoplasmic domain.

So, rather than serving only as a Netrin-binding signalling protein on the surface of growing neurons, Frazzled, and possibly other DCC-family members, also helps Netrin to steer axons that do not themselves express Frazzled. The extracellular domain of Frazzled captures and immobilizes Netrin on regions encountered by extending axons (Fig. 1b). This process does not require intracellular signalling events triggered by the binding of Netrin to Frazzled. It is well established that axons can respond both *in vitro* and *in vivo* to smooth gradients of guidance cues. But Hiramoto *et al.*[1] have uncovered an elegant mechanism that avoids problems inherent in using the free diffusion of cues to precisely control guidance events at a distance.

These results imply that an as yet uncharacterized receptor on the growing axon must be responding to Netrin. Netrin appears to be acting as an attractant, so *Drosophila* UNC-5 seems an unlikely candidate for this receptor. And does Netrin alone, or a Netrin–Frazzled complex, function as the ligand for the guidance events described by Hiramoto and colleagues? Is the Frazzled-bound form of Netrin active, or does Netrin signal only when released from Frazzled, subject to the off-rate of this reaction? The possibility that a Netrin–Frazzled complex may be transported to the final site of Netrin accumulation also deserves serious consideration. Finally, given that other secreted guidance cues unrelated to Netrin may be similarly localized, we must be prepared to accept new roles for old guidance receptors. ■

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