HIGHLIGHTS

SIGNALLING

Repulsive or attractive?

For neuronal networks to form correctly during development, nerve growth cones must respond precisely to extracellular guidance factors such as netrin-1. The repulsive and attractive guidance of axons by extracellular guidance factors is modulated by the intracellular second messengers cyclic nucleotides and Ca^{2+}. But how do these signalling molecules interact to determine the polarity of the guidance response? In *Nature*, Hong and colleagues now provide insights.

A netrin-1 gradient induces the attraction of *Xenopus* spinal neuron growth cones when it acts through its receptor deleted-in-colorectal-cancer (DCC). However, when another netrin-1 receptor, UNC5, is present, netrin-1 induces repulsion by acting through the DCC–UNC5 receptor complex. So, what are the intracellular signals that underlie these responses?

The authors first examined the effects of cAMP and cGMP signalling on DCC-mediated attraction in control neurons, and on DCC–UNC5-mediated repulsion in neurons overexpressing UNC5. Using a cGMP analogue and inhibitors of PKA (cAMP-dependent protein kinase) and PKG (cGMP-dependent protein kinase), they showed that cGMP signalling has an important regulatory role in netrin-1-induced repulsion, whereas cAMP signalling modulates both DCC-mediated attraction and DCC–UNC5-mediated repulsion.

Next, Hong and co-workers studied the relative roles of cAMP and cGMP in netrin-1-mediated growth-cone guidance. They varied the ratio of a cAMP and a cGMP analogue, and found that the growth-cone turning response correlated with this ratio; a high cAMP:cGMP ratio favoured attraction, whereas a low ratio favoured repulsion. But how does this ratio modulate netrin-1 signals?

Netrin-1-induced attraction requires Ca^{2+} entry through channels such as L-type Ca^{2+} channels (LCCs), which are activated by cAMP and inactivated by cGMP signalling pathways. Hong and colleagues found that netrin-1 increased the amplitude of LCC-mediated Ca^{2+} currents in control growth cones, whereas it decreased these currents in UNC5-overexpressing growth cones. Furthermore, they showed that a cGMP analogue and a PKA inhibitor decreased the Ca^{2+} currents in control neurons, and that a PKG inhibitor rescued these currents in UNC5-overexpressing neurons. These results indicate that cyclic-nucleotide signalling modulates LCC activity in nerve growth cones.

So, in the model proposed by Hong and co-workers, netrin-1 activation of DCC leads to the activation of LCCs. DCC activation also leads to the activation of cAMP signalling, which, in turn, enhances LCC activity. This results in increased Ca^{2+} currents and growth-cone attraction. In the presence of UNC5, netrin-1 activation of DCC–UNC5 also activates cGMP signalling. This results in decreased Ca^{2+} currents and growth-cone repulsion. This work has therefore shown that interactions between cyclic nucleotide and Ca^{2+}-signalling pathways are crucial for netrin-1-mediated axon guidance, and that the regulation of Ca^{2+} channels is an important early event in the transduction of netrin-1 signals.

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References and links

ORIGINAL RESEARCH PAPER

Nishiyama, M. *et al.* Cyclic AMP/GMP-dependent modulation of Ca^{2+} channels sets the polarity of nerve growth-cone turning. *Nature* 2003 June 26 (DOI: 10.1038/nature01751)