AXON GUIDANCE

The turning point

Engrailed 2 (En2), a homeodomain transcription factor, is expressed in a caudal-to-rostral gradient in the developing tectum. This is thought to be crucial for setting up the gradients of axon guidance cues that are important for topographic map formation in the vertebrate visual system. However, the results of a new study show that En2 can also affect axon turning by interacting with the translational machinery in the growth cone.

En2 contains a few protein domains involved in nuclear export, secretion and internalization, and can be secreted and transferred from one cell to another. These features are unorthodox for a transcription factor and have long intrigued researchers. Brunet and colleagues set out to solve this mystery and tested the effect of an En2 gradient on axon turning *in vitro*.

Interestingly, *Xenopus* nasal axons were attracted by En2, whereas temporal axons were repelled. These opposite turning responses correspond to the *in vivo* organization of the retinotectal map, in which nasal axons terminate in the En2-rich caudal tectum but temporal axons avoid it. En2 was rapidly internalized by living growth cones. This process seems to be crucial for the effect of En2 on axon turning, as a mutant form of En2 that was defective in internalization also had no effect on growth cones.

Next, the researchers studied whether the turning responses required involvement of the cell body and whether gene expression and protein synthesis were necessary. Nasal growth cones transected from their cell bodies still turned towards an En2 gradient, and isolated temporal growth cones continued to turn away from this gradient. These responses were blocked by protein synthesis inhibitors, but not transcription inhibitors, which indicates that nascent protein synthesis in the growth cone is necessary for its turning responses to En2.

But how does En2 regulate the translational machinery in the growth cone? Like many other homeodomain proteins, En2 contains a highly conserved binding site to enkaryotic initiation factor 4E (eIF4E) that is typically found in translational machinery. En2 can bind to eIF4E, and Brunet *et al.* showed that a mutant form of En2 that lacks the putative eIF4E-binding domain did not attract nasal axons. In addition, En2 triggered rapid phosphorylation of eIF4E and eIF4E-binding protein (4E-BP1). It is thought that 4E-BP1 silences translation by competitively binding to eIF4E and sequestering it from the translation initiation complex. Phosphorylation of 4E-BP1 releases eIF4E, which, on phosphorylation, becomes activated and initiates translation.

This elegant study has unravelled a new mechanism whereby the concentration gradient of En2 is used to guide axon growth. Whether other transcription factors have a similar role remains to be seen.

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ORIGINAL RESEARCH PAPER Brunet, I. *et al.* The transcription factor Engrailed-2 guides retinal axons. *Nature* **438**, 94–98 (2005)
FURTHER READING Prochiantz, A. & Joliot, A. Can transcription factors function as cell–cell signalling molecules? *Nature Rev. Mol. Cell Biol.* **4**, 814–819 (2003)
WEB SITE Holt's laboratory: http://www.anat.cam.ac.uk/staff/holt/