AXON GUIDANCE

Pioneering exit

Guidance information for axonal growth cones is provided either by extracellular signalling molecules or by axon–axon interactions with neurons that have previously taken the same path, termed pioneer axons. As the role of pioneer axons in guiding large vertebrate axon tracts remains largely unknown, Chien and colleagues studied these axons in the retinotectal system of Zebrafish; they found that isotypic axon–axon interactions are necessary and sufficient for pathfinding.

The authors specifically prevented the development of early-born retinal ganglion cells (RGCs) by injecting a translation-blocking antisense morpholino oligonucleotide (MO) against *ath5* mRNA (which encodes a cell-autonomous transcription factor that is required for RGC differentiation) at the one-cell stage of the embryo.

They found that administration of a high dosage of *ath5*MO prevented the RGCs from differentiating until 42 hours post-fertilization. Furthermore, the axons of later-born RGCs failed to exit the eye through the optic nerve, suggesting that isotypic pioneer–follower interactions are required for later-born RGCs to exit the eye.

When donor RGCs were grafted into *ath5*MO-injected hosts, pioneer donor axons and later-born host axons were both found to exit the eye and reach the tectum, suggesting that early-born RGCs are sufficient to guide the axons from later-born RGCs.

Next the authors tested the effect of the pioneer and host genotype on pathfinding. When donor RGCs from *astray* (*ast*) mutants, which normally make severe pathfinding errors because they lack the Robo2 receptor, were grafted into wild-type hosts, pioneer *ast*-axons navigated better than expected. Surprisingly, wild-type donors grafted into *ast*-mutants made lots of pathfinding mistakes, indicating that the host genotype influences the behaviour of the pioneers. When the host early-born RGCs were ablated with *ath5*MO in these experiments, the genotype of the donor pioneers affected the pathfinding of the host followers.

This study demonstrates that isotypic pioneer–follower interactions are required in pathfinding along the retinotectal path and are likely to co-operate with other guidance mechanisms. Future studies will shed light on the factors that distinguish pioneers from followers and those that underlie the critical period.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Pittman, A. J., Law, M.-Y. & Chien, C.-B. Pathfinding in a large vertebrate axon tract: isotypic interactions guide retinotectal axons at multiple choice points. *Development* **135**, 2865–2871 (2008)