NEURAL DEVELOPMENT

Lipid guideposts

Various proteins act as spatial cues in axon guidance, but whether lipids can serve a similar function has been unclear. A new study now shows that a glial cell-derived glycerophospholipid acts as a repulsive spatial cue during the pathfinding of nociceptive axons in the embryonic spinal cord of chicks and mice.

The membranes of rodent radial glia have been found to contain the glycerophospholipid phosphatidyl-β-D-glucoside (PtdGlc). In line with this finding, here, Guy *et al.* found that the large majority of proliferating glia that were isolated from the chick embryo spinal cord showed co-immunolabelling for PtdGlc and transitin, which is a marker of radial glia. Such co-staining was also observed in chick embryo spinal cord sections, with no detection of PtdGlc in neurons. In the medium in which isolated glia were cultured, the authors detected a water-soluble derivative of PtdGlc — LysoPtdGlc — suggesting that these radial glia produce PtdGlc and release its derivative into the extracellular space.

As developing dorsal root ganglion (DRG) axons of sensory neurons enter the spinal cord, they become segregated, with proprioceptive axons assuming a dorsomedial position and nociceptive axons being found in a lateral position. The authors found that, in sections of the embryonic chick spinal cord, PtdGlc and LysoPtdGlc (detected by immunolabelling and mass spectrometry, respectively) were enriched in the dorsomedial spinal cord, and that neurotrophin 3 (NT3)-responsive proprioceptive axons (detected by immunolabelling of tropomyosin-related kinase C (TRKC), an NT3 receptor), but not nerve growth factor (NGF)-responsive nociceptive axons (identified by the expression of TRKA, an NGF receptor), extended into this area.

Interestingly, in co-culture experiments, the presence of dorsomedial (but not dorsolateral) spinal cord sections repelled the growth of NGF-responsive (but not NT3-responsive) axons from DRG explants, and this repulsive effect could be attenuated by application of a LysoPtdGlc-specific antibody. Moreover, synthetic LysoPtdGlc or LysoPtdGlc derived from spinal cord-isolated PtdGlc also selectively repelled NGF-responsive axons in DRG neuron cultures. Finally, chick embryos injected with the LysoPtdGlc-specific antibody showed aberrant TRKA-positive axon projections in the dorsomedial spinal cord. Thus, these data show that LysoPtdGlc has an important role in nociceptive-axon pathfinding.

How does LysoPtdGlc mediate repulsion? The authors found that inhibition of RHO signalling or of $G_{\alpha 13}$ blocked LysoPtdGlc-induced chemorepulsion of NGF-responsive axons, indicating the involvement

of a G protein-coupled receptor (GPCR) in the mechanism. *In vitro* screening of 115 GPCRs revealed only one LysoPtdGlc-responsive receptor: GPR55. Together, these findings suggest that LysoPtdGlc binds to GPR55, in turn activating $G_{\alpha 13}$ and RHO signalling to mediate nociceptive-axon repulsion.

In support of this assertion, the authors confirmed that GPR55 was expressed in mouse DRG neurons, and showed *in vitro* that LysoPtdGlc could repel NGF-responsive DRG axons from wild-type mice but not from *Gpr55*-knockout animals. Moreover, NGF-responsive axons in the spinal cord of embryonic *Gpr55*-knockout mice aberrantly projected to a dorsomedial position.

Together, these findings reveal a glial phospholipid-mediated axon guidance mechanism in chicks and mice that is essential for proper nociceptive neural development in the spinal cord.

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