<Further Development 17_14>

Intraretinal Guidance: How Do RGC Axons Even Leave the Eye in the Right Place?

The adhesion and growth of retinal ganglion cell (RGC) axons along the inner surface of the retina may be governed by the retina's laminin-containing basal lamina. The embryonic lens and the periphery of the retina secrete inhibitory factors (probably chondroitin sulfate proteoglycans) that repel the RGC axons, preventing them from traveling in the wrong direction (Figure 1; Hynes and Lander 1992; Ohta et al. 1999). Neural cell adhesion molecule (NCAM) may also be especially important here because the directional migration of the retinal ganglion growth cones depends on the NCAM-expressing glial endfeet at the inner retinal surface (Stier and Schlosshauer 1995). In the mouse retina, RGCs express Robo1 and Robo2 receptors, and Slits are expressed in both the ganglion layer and lens epithelium. Functional analysis of Slit and Robo during *intraretinal* pathfinding of RGC axons suggests that Slits and Robo2 play a role in repelling RGC axons out of the retina (Niclou et al. 2000; Thompson et al. 2006, 2009). The secretion of netrin-1 by the cells of the optic disc (where the axons are assembled to form the optic nerve) plays a role in this migration, as well. Mice lacking the genes for either netrin-1 or for the netrin receptor (found in the retinal ganglion axons) have poorly formed optic nerves because many of the axons fail to leave the eye and instead grow randomly around the disc (Deiner et al. 1997). The role of netrin may change in different parts of the eye. At the entrance to the optic nerve, netrin-1 is co-expressed with laminin on the surface of the retina. Laminin converts netrin from having an attractive signal to having a repulsive signal. This repulsion might "push" the growth cone away from the retinal surface and into the head of the optic nerve, where netrin is expressed without laminin (Mann et al. 2004; see Figure 1).

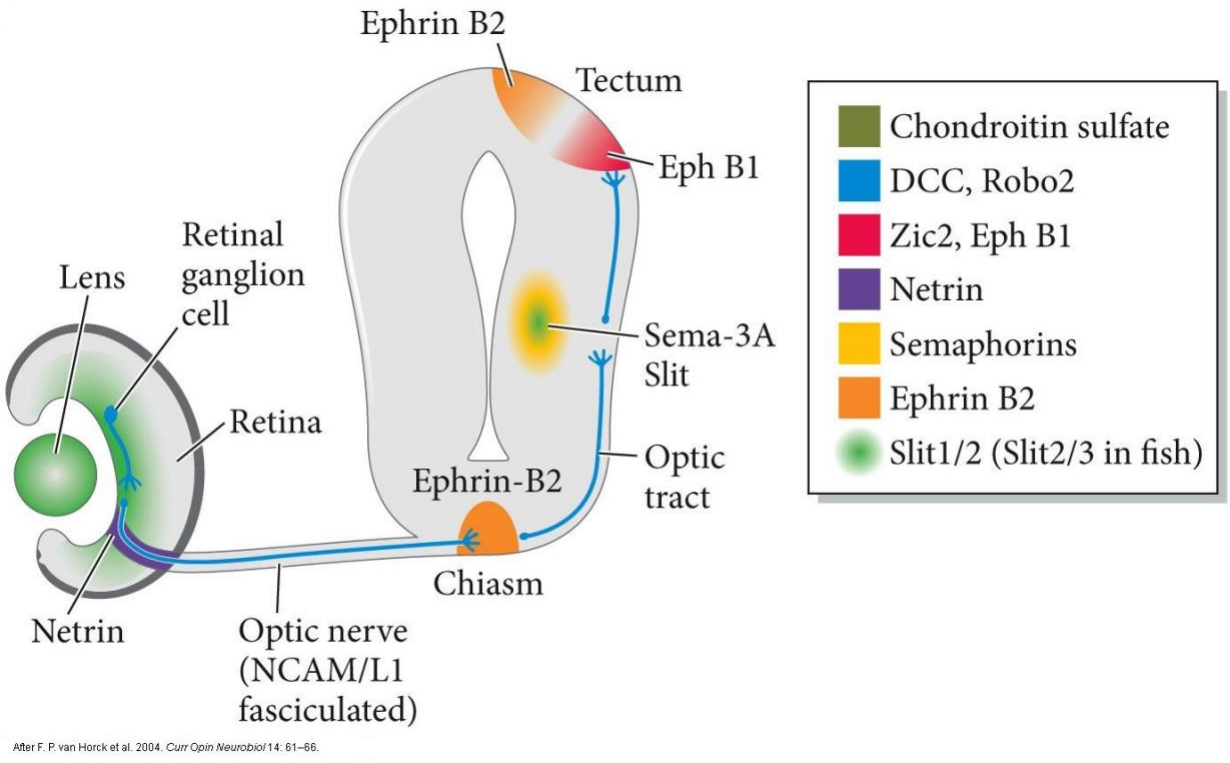

Figure 1 Multiple guidance cues direct the movement of retinal ganglion cell (RGC) axons to the optic tectum. Guidance molecules belonging to the netrin, Slit, semaphorin, and ephrin families are expressed in discrete regions at several sites along the pathway to direct the RGC growth cones. RGC axons are repelled from the retinal periphery, probably by chondroitin sulfate. At the optic disc, the axons exit the retina and enter the optic nerve, guided by netrin/DCC-mediated attraction. Once in the optic nerve, the axons are kept within the pathway by inhibitory interactions. Slit proteins in the optic chiasm create zones of inhibition. Zic2-expressing ganglia in the ventrotemporal retina project Eph B1-expressing axons, which are repelled at the chiasm by ephrin B2, thus terminating at ipsilateral (same-side) targets. Neurons from the medial portions of the retina do not express Eph B1 and proceed to the opposite (contralateral) side. Cross-sectional view. Not all cues are shown.

Upon their arrival at the optic nerve, the migrating axons fasciculate (form a bundle) with axons already present there. NCAM and L1 cell adhesion molecules are critical to this fasciculation, and antibodies against L1 or NCAM cause the axons to enter the optic nerve in a disorderly fashion, which in turn causes them to emerge into the tectum at the wrong positions (Thanos et al. 1984; Brittis et al. 1995; Yin et al. 1995).

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