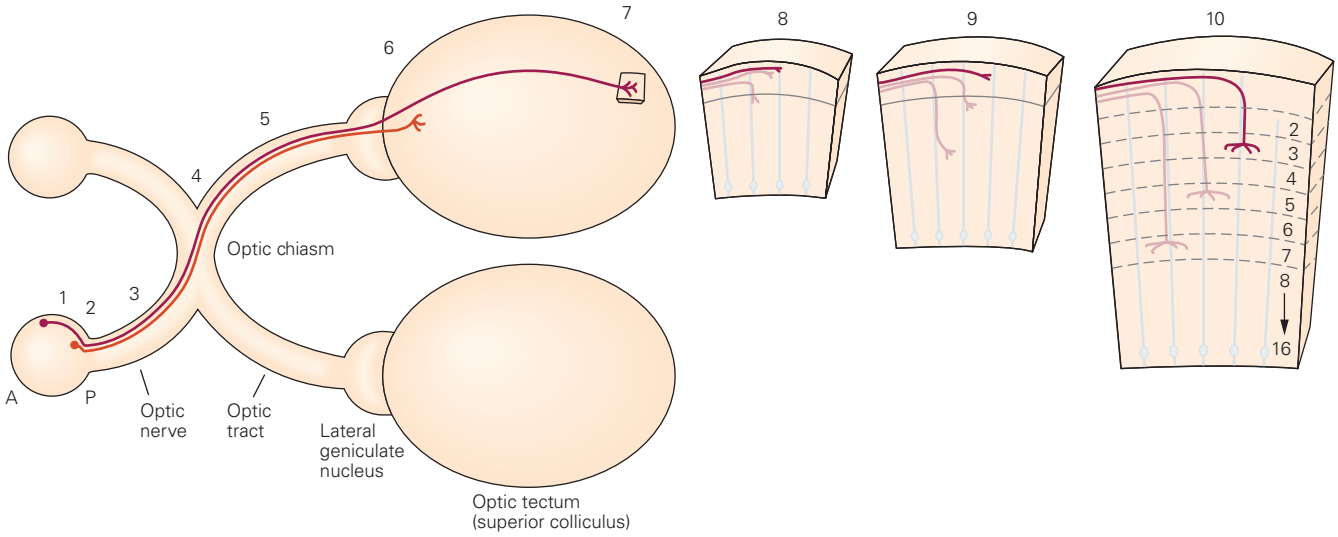

Figure 47–12 The axons of retinal ganglion cells grow to the optic tectum in discrete steps. Two neurons that carry information from the nasal half of the retina are shown. The axon of one crosses the optic chiasm to reach the contralateral optic tectum. The axon of the other also crosses the optic chiasm but projects to the lateral geniculate nucleus. The numbers indicate important landmarks on the axon's journey. The growing axon is directed toward the optic nerve head (the junction of the nerve with the retina) (**1**), enters into the optic nerve (**2**), extends through the optic nerve (**3**), swerves to remain ipsilateral (not shown) or crosses to the contralateral side at the optic chiasm (**4**), extends through the optic tract (**5**), enters into the optic tectum or lateral geniculate nucleus (not shown) (**6**), navigates to an appropriate rostrocaudal and dorsoventral position on the tectum (**7**), turns to enter the neuropil (descends in chicks as shown here; ascends in mammals) (**8**), stops at an appropriate layer where a rudimentary terminal arbor is formed (**9**), and finally is remodeled (**10**). (Abbreviations: **A**, anterior; **P**, posterior).

colliculus, and small numbers project to the pulvinar, superchiasmatic nucleus, and pretectal nuclei. Within these targets, different retinal axons project to different regions. As Sperry showed, the retinal axons form a precise retinotopic map on the tectal surface. Similar maps form in other areas innervated by retinal axons such as the lateral geniculate nucleus.

Having reached an appropriate position within the tectum, retinal axons need to find an appropriate synaptic partner. To achieve this last leg of their journey, retinal axons turn and dive into the tectal neuropil (Figure 47–12), descending (or, in mammals, ascending) along the surface of radial glial cells, which provide a scaffold for radial axonal growth. Although radial glial cells span the entire extent of the neuroepithelium, each retinal axon confines its synaptic terminals to a single layer. The dendrites of many postsynaptic cells extend through multiple layers and form synapses along their entire length, but retinal inputs are restricted to a small fraction of the target neuron's dendritic tree. These organizational features imply that layer-specific cues arrest axonal elongation and trigger arborization.

The problem of long-distance axon navigation is therefore solved by dividing the journey into short segments in which intermediate targets guide the axons along the path to their final targets. Some intermediate targets, such as the optic chiasm, are "decision" regions where axons diverge.

Reliance on intermediate targets is an effective solution to the problem of long-distance axonal navigation but is not the only one. In some cases, the first axons reach their targets when the embryo is small and the distance to be covered is short. These "pioneer" axons respond to molecular cues embedded in cells or the extracellular matrix along their way. The first axons to exit the retina fall within this class. Axons that appear later, when distances are longer and obstacles more numerous, can reach their targets by following the pioneers. Yet another guidance mechanism is a molecular gradient. Indeed, as we will see, gradients of cell-surface molecules in the tectum inform axons about their proper termination zone.

Gradients of Ephrins Provide Inhibitory Signals in the Brain

So far, we have seen how retinal axons reach the tectum by responding to a series of discrete directional cues. However, these choices during growth do not account

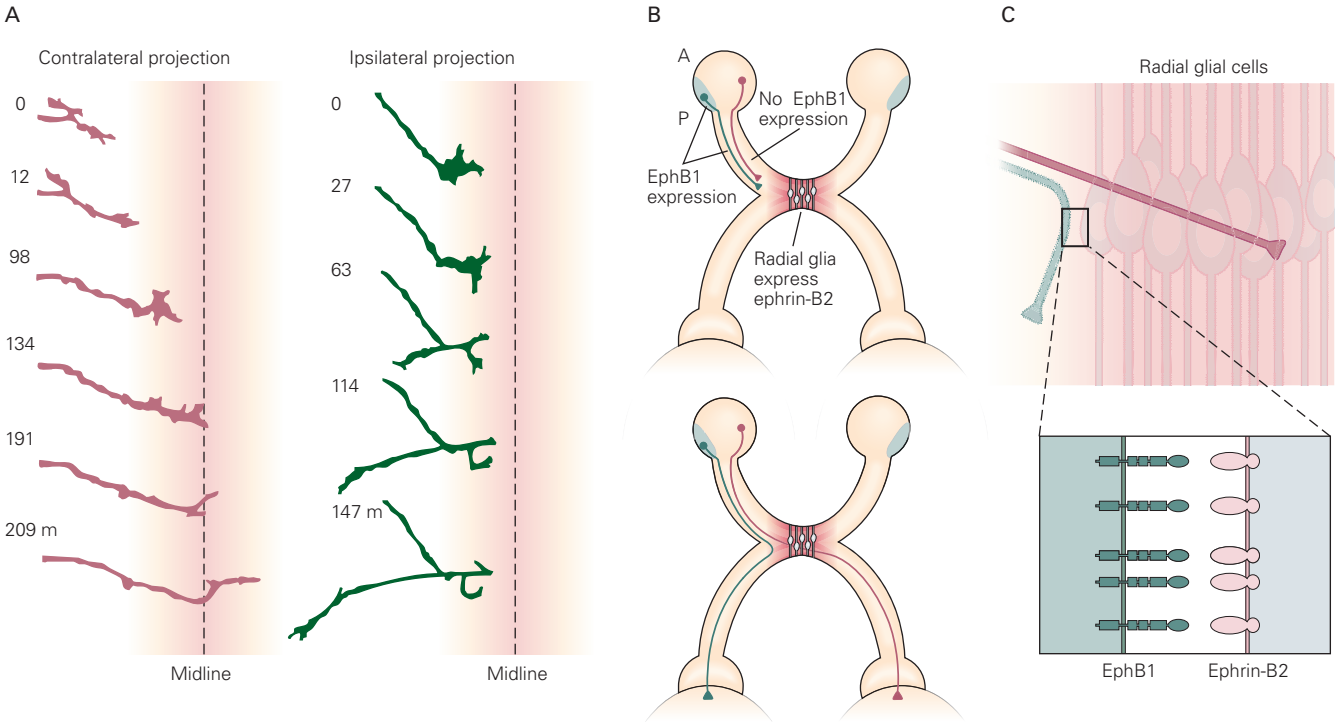

Figure 47–13 Axons of retinal ganglion neurons diverge as they reach the optic chiasm.

A. A time lapse series shows axons approaching the midline. Axons that arise from the nasal hemiretina cross the optic chiasm and project to the contralateral tectum (*left*). In contrast, axons from the temporal hemiretina reach the chiasm but fail to cross and thus project toward the ipsilateral tectum (*right*). (Reproduced, with permission, from Godement, Wang, and Mason 1994.)

B. The axons of neurons from the temporal hemiretina, which express the tyrosine kinase receptor EphB1, encounter ephrin-B2 expressed by midline radial glial cells at the optic chiasm and so are prevented from crossing the midline. The axons of nasal hemiretina neurons, which lack EphB1 receptors, are unaffected by the presence of ephrin-B2 and cross to the contralateral side. (Abbreviations: **A**, anterior; **P**, posterior.)

C. Higher-power view illustrating the trajectories of retinal ganglion cell axons at the chiasm.

for the smoothly graded connections implied by Sperry's analysis of the retinotopic map in the tectum. The quest for the hypothetical "map molecules" became a major focus for developmental neurobiologists, and so we describe it in some detail.

A key breakthrough in the quest for these molecules came with the development of bioassays in which explants from defined portions of the retina were laid on substrates of tectal membrane fragments. The membrane fragments were taken from defined anteroposterior portions of the tectum and arranged in alternating stripes. Axons from the temporal (posterior) hemiretina were found to grow preferentially on membranes from anterior tectum, a preference similar to that exhibited in vivo (Figure 47–14). This preference was found to result from the presence of inhibitory factors in posterior membranes rather than from attractive or adhesive substances in anterior membranes. This observation was one of the first to demonstrate the role of inhibitory or repellent substances in axon guidance.

This stripe assay permitted the characterization of an inhibitory cue, present in membranes from the posterior but not the anterior tectum. Independently, molecular biologists identified a family of receptor tyrosine kinases, the Eph kinases, and a large family of membrane-associated ligands, the ephrins. Both receptors and ligands are divided into A and B subfamilies. The ephrin-A proteins bind and activate EphA kinases; conversely, ephrin-B proteins bind and activate EphB kinases (Figure 47–11C).

The two lines of research converged when the tectal inhibitory cue was identified as ephrin-A5. We now know that the Eph kinases and ephrins serve many functions in neural and nonneural tissues and that each class of proteins can serve as ligands or receptors, depending on cellular context. In the developing

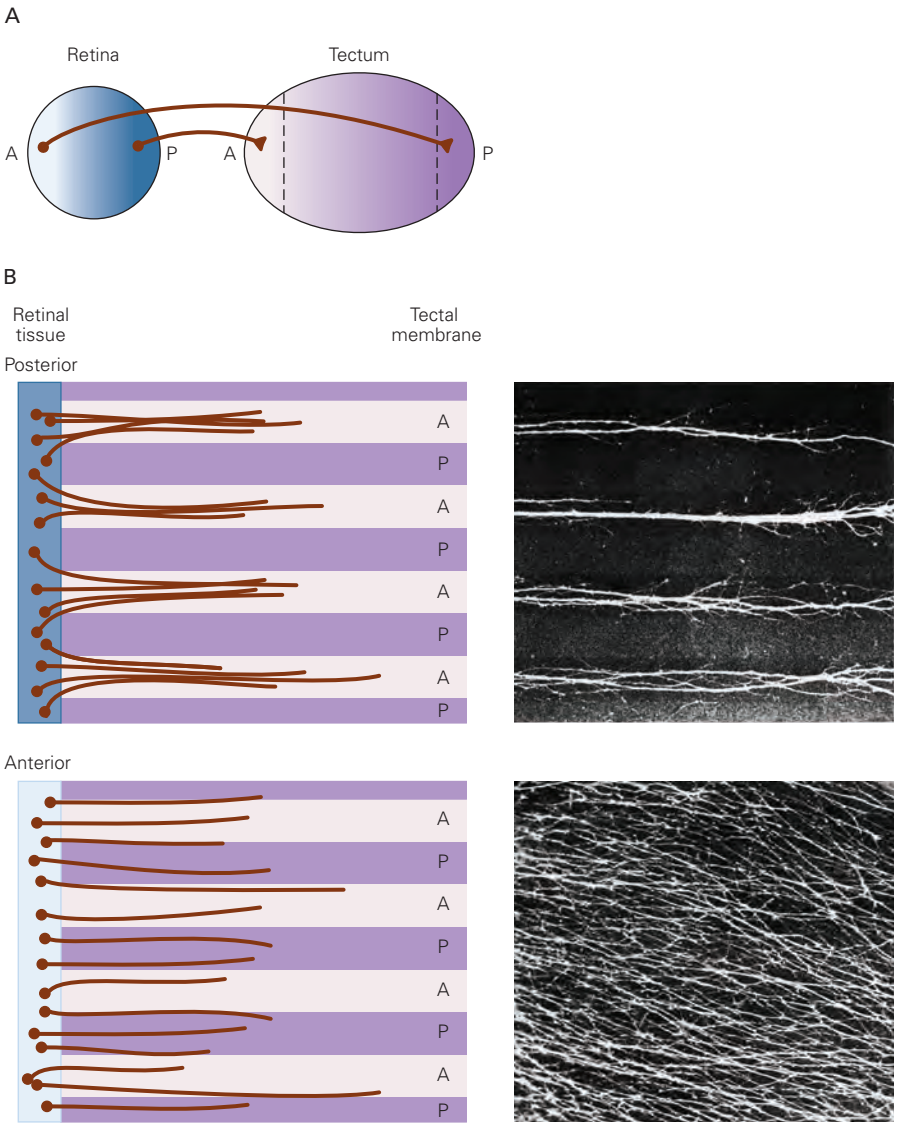

Figure 47–14 Repellent signals guide developing retinal axons in vitro.

A. Retinal ganglion axons from the posterior (temporal) hemiretina project into the anterior developing tectum. Conversely, axons from the anterior (nasal) hemiretina project into the posterior tectum.

B. Fragments of membrane were taken from specified anteroposterior portions of the tectum and arranged in alternating strips. Axons from explants of posterior retina grow selectively on the fragments from anterior tectum. The preferential growth of axons on anterior membrane results from an inhibitory cue in the posterior membrane. In contrast, axons from anterior retina grow on both anterior and posterior tectal membrane fragments. (Abbreviations: A, anterior; P, posterior.) (Adapted, with permission, from Walter, Henke-Fahle, and Bonhoeffer 1987.)

nervous system, these proteins comprise a major group of repellent signals.

Ephrin–Eph interactions account in large part for formation of the retinotopic map in the tectum. Levels of ephrin-A2 and ephrin-A5 in the tectum as well as levels of the Eph receptors in the retina are graded along the anteroposterior axis. These gradients run in the same direction. Ephrin-A concentrations run from posterior-high to anterior-low in tectum, while Eph A concentrations run from posterior-high to anterior-low in retina (Figure 47–15A). Such counter-gradients account, at least in part, for topographic mapping. Axons from posterior retinal ganglion cells with high levels of EphA receptors are repelled most strongly by the high level of ephrin-A in the posterior tectum and thus are confined to the anterior tectum. The less sensitive axons from the anterior retina are able to penetrate further into the posterior domain of the tectum. Ephrin-A2 and ephrin-A5 are therefore strong candidates for chemospecificity factors of the type postulated by Sperry.

The crucial role of the interaction of ephrins and Eph kinases in the formation of retinotopic maps has been confirmed in vivo. Overexpression of ephrin-A2 in the developing optic tectum of chick embryos generates small patches of cells in the rostral tectum that are abnormally rich in ephrin-A2. Temporal retinal axons, which normally avoid the ephrin-rich caudal tectum, also avoid these patches in the rostral tectum, and they terminate in abnormal positions. In contrast, nasal retinal axons, which normally grow toward the

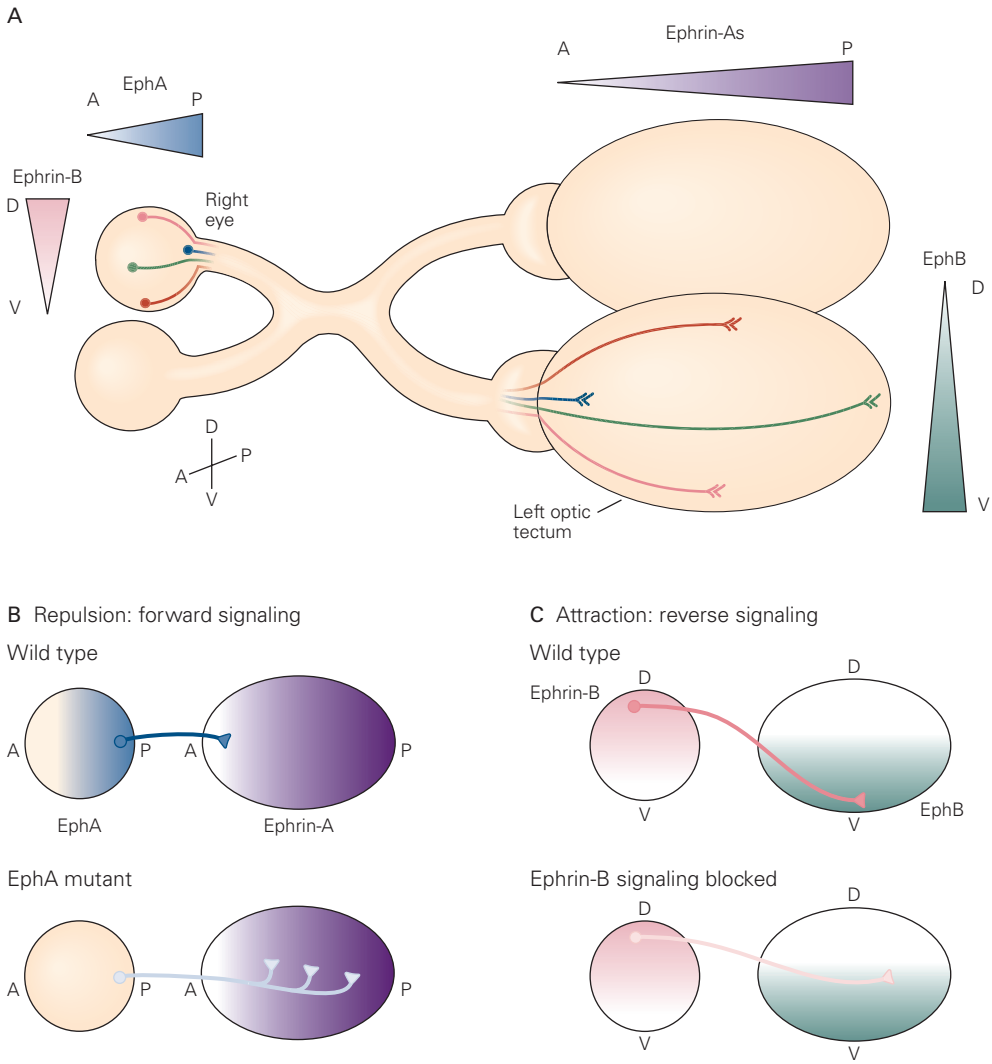

Figure 47–15 The formation of retinotopic maps in vivo depends on ephrin-Eph kinase signaling.

A. In the retina, EphA receptors are expressed in an anteroposterior (**A-P**) gradient, and ephrin-B is expressed in a dorsoventral (**D-V**) gradient. In the tectum, ephrin-A receptors are distributed in an anteroposterior gradient and EphB in a dorsoventral gradient.

B. Expression of EphA in retinal axons that derive from neurons in the posterior (temporal) retina directs axon growth to the anterior tectum through avoidance of ephrin-A proteins. In EphA mutant mice, posterior retinal axons are able to project to a more posterior domain within the tectum.

C. EphB signaling directs the projection of dorsal retinal axons to the ventral tectum. Blocking ephrin-B signaling with soluble EphB protein causes dorsal axons to project to an abnormally dorsal domain within the tectum.

caudal tectum, are not perturbed by encounters with excess ephrin-A.

Conversely, in mice with targeted mutations in the relevant *ephA* or *ephrin-A* genes, some posterior retinal axons terminate in inappropriately posterior tectal regions (Figure 47–15B). Anterior retinal axons, which naturally express low levels of EphA proteins, project normally in these mutants. In mice lacking both ephrin-A proteins, these deficits are more severe than with either single mutant. Thus, the interaction of ephrin-A with EphA receptors is crucial for the targeting of retinal axons in the tectum. These ephrin/EphA pairs possess the properties of the recognition molecules that Sperry predicted were necessary to direct

topographic mapping along the anteroposterior axis of the tectum.

Of course, the retinal map also has a dorsoventral axis. Ephrin/EphB pairs are involved in establishing order along this axis. Just as ephrin-A and EphA are graded along the anteroposterior axis, ephrin-B and EphB are graded along the dorsoventral axis, and manipulation of ephrin-B and EphB levels affects dorsoventral mapping (Figure 47–15C). Thus, at a simple level, the retinotopic map is arranged in rectangular coordinates with ephrin-A/EphA and ephrin-B/EphB labeling the anteroposterior and dorsoventral axes, respectively.

Although this simple view is satisfying, the reality is more complex. First, EphB kinases are expressed in the tectum as well as in the retina, and ephrins-A are expressed in the retina as well as in the tectum. Thus, so-called "*cis*" interactions (Eph and ephrin on the same cell) as well as "*trans*" interactions (Eph on growth cone, ephrin on target cell) may be involved. Second, both ligands and receptors are present at multiple points along the optic pathway and play multiple roles. As we have seen, ephrin-B/EphB interactions affect not only dorsoventral mapping but also the decision of an axon to cross to the contralateral side at the optic chiasm. Finally, in developing visual circuits, more precise spatial mapping of retinal inputs is regulated by patterns of neural activity, as discussed in the next two chapters. Nonetheless, we now have the outline of a molecular strategy for the initial formation of topographic projections from the eye to the brain.

Axons From Some Spinal Neurons Are Guided Across the Midline

One of the fundamental features of the central nervous system is the need to coordinate activity on both sides of the body. To accomplish this task, certain axons need to project to the opposite side.

We have seen one example of axonal crossing in the optic chiasm. Another example that has been studied in detail is the axonal crossing of *commissural neurons* that convey sensory information from the spinal cord to the brain at the ventral midline of the spinal cord across the floor plate. After crossing, axons turn abruptly and grow up toward the brain. This simple trajectory raises several questions. How do these axons reach the ventral midline? How do they cross the midline, and after crossing, how do they *ignore* cues that axons on the other side are using to get to the midline? In other words, why do they turn toward the brain instead of crossing back?

Netrins Direct Developing Commissural Axons Across the Midline

Many of the neurons that send axons across the ventral midline are generated in the dorsal half of the spinal cord. The first task for these axons is to reach the ventral midline. Ramón y Cajal considered the possibility that chemotactic factors emitted by targets could attract axons, but this idea lay dormant for nearly a century. We now know that such factors do exist, and one of them, the protein netrin-1, is expressed by cells of the floor plate as well as by progenitors along the ventral midline. When presented in culture, netrin attracts commissural axons; when mice are deprived of netrin-1 function, axons fail to reach the floor plate (Figure 47–16). It may act as both a secreted factor (chemotaxis) and a membrane guidance molecule (haptotaxis) to guide the axons of commissural neurons to the floor plate.

The netrin protein is structurally related to the protein product of *unc-6*, a gene shown to regulate axon guidance in the nematode *Clostridia elegans.* Two other *C. elegans* genes, *unc-5* and *unc-40*, encode receptors for the unc-6 protein. Vertebrate netrin receptors are related to the unc-5 and unc-40 receptors. The unc-5H proteins are homologs of unc-5, and DCC (deleted in colorectal cancer) are related to unc-40 (see Figure 47–11G). These receptors are members of the immunoglobulin superfamily, and their functions have been remarkably conserved throughout animal evolution (Figure 47–17). This conservation supports the use of simple and genetically accessible invertebrates to unravel developmental complexities. In no area has this approach been more fruitful than in the analysis of axon guidance. Dozens of genes that affect this process were first identified and cloned in *Drosophila* and *C. elegans* and then shown to play important and related roles in mammals.

Chemoattractant and Chemorepellent Factors Pattern the Midline

Other signaling systems work with netrins to guide commissural axons. One group consists of bone morphogenetic proteins, which are secreted by the roof plate. They act as repellents, directing commissural axons ventrally as they begin their journey. Additional factors from the floor plate, such as the hedgehog proteins initially involved in patterning the spinal cord (Chapter 45), may collaborate with netrins at a later stage, serving as axonal attractants.

Once commissural axons reach the midline, they find themselves exposed to the highest available levels

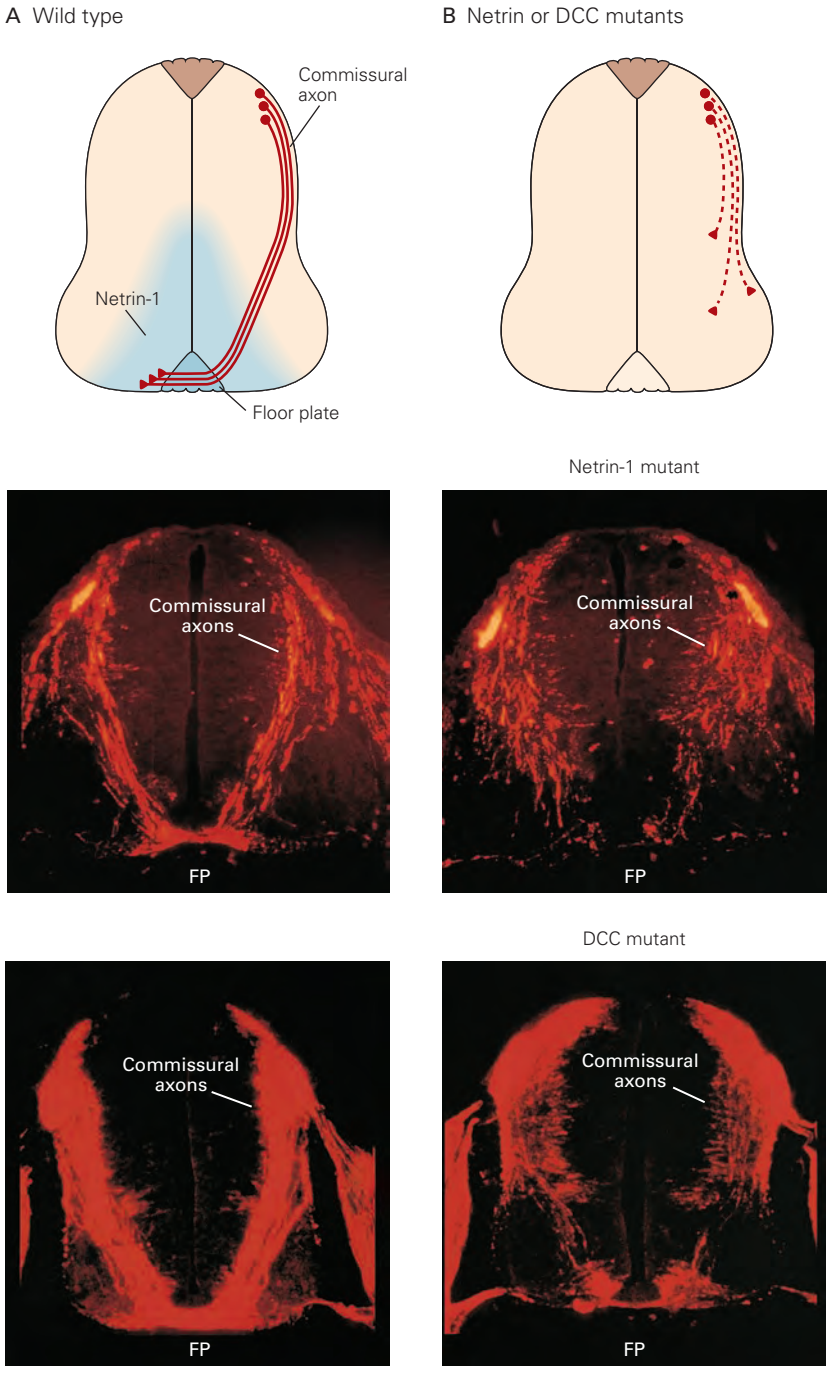

Figure 47–16 Netrin signaling attracts the axons of spinal commissural neurons to the floor plate. (Micrographs reproduced, with permission, from Marc Tessier-Lavigne.)

A. Netrin-1 is generated by floor plate cells and ventral neural progenitors. It attracts the axons of commissural neurons to the floor plate (**FP**) at the ventral midline of the spinal cord.

B. Most commissural axons fail to reach the floor plate when netrin or deleted in colorectal cancer (**DCC**) proteins are eliminated.

of netrin-1 and sonic hedgehog. Yet this netrin-rich environment does not keep the axons at the midline indefinitely. Instead they cross to the other side of the spinal cord, even while their contralateral counterparts are navigating up the netrin chemoattractant gradient.

This puzzling behavior is explained by the fact that growth cones change their responsiveness to attractive and repellent signals as a consequence of exposure to floor plate signals. This switch illustrates an important property of intermediate targets involved in axon guidance. Factors presented by intermediate targets not only guide the growth of axons but also change the sensitivity of the growth cone, preparing it for the next leg of its journey.

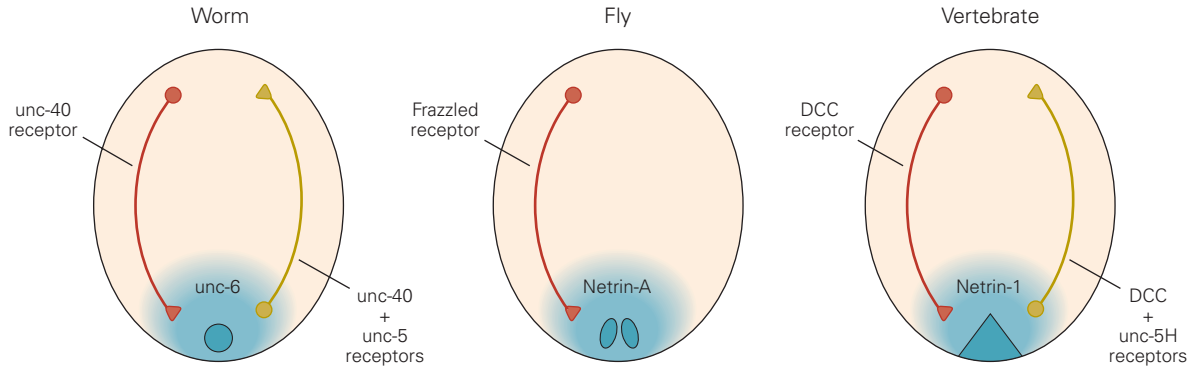

Figure 47–17 **The expression and activity of netrins have been conserved throughout evolution.** Netrins are secreted by ventral midline cells in worms, flies, and vertebrates and interact with receptors on cells or axons that migrate or extend along the dorsoventral axis. The netrin receptors unc-40 (worm), frazzled (fly), and deleted in colorectal cancer (**DCC**) (vertebrate) mediate netrin's attractant activity, whereas unc-5 class receptors mediate its repellent activity.

Once axons arrive at the floor plate, they become sensitive to Slit, a chemorepellent signal secreted by floor plate cells (Figure 47–18). Before commissural axons reach the floor plate, the Robo proteins that serve as Slit receptors are kept inactive by expression of a related protein, Rig-1. As axons reach the floor plate, levels of Rig-1 on their surface decline, unleashing Robo activity and causing axons to respond to the repellant actions of Slit. This repellent action propels growth cones *down* the Slit gradient into the contralateral side

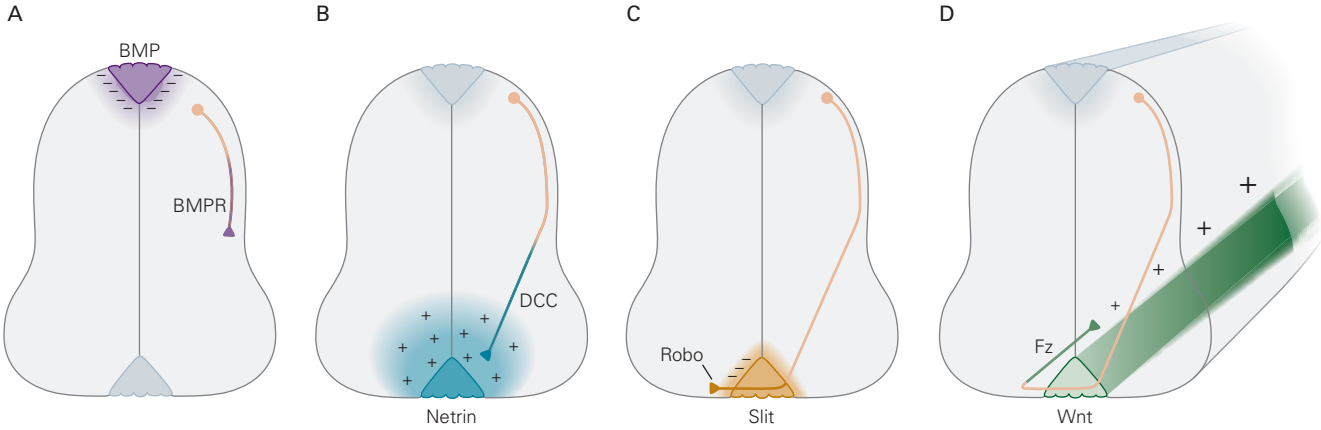

Figure 47–18 **Guidance cues expressed by roof plate and floor plate cells guide commissural axons in the developing spinal cord.**

A. Bone morphogenetic proteins (**BMP**) secreted by roof plate cells interact with BMP receptors (**BMPR**) on commissural axons to direct the axons away from the roof plate.

B. Netrin expressed by floor plate cells attracts deleted in colorectal cancer (**DCC**)-expressing commissural axons to the ventral midline of the spinal cord. Sonic hedgehog has also been implicated in the ventral guidance of commissural axons.

C. Slit proteins secreted by floor plate cells interact with Robo receptors on commissural axons to prevent these axons from recrossing the midline. Prior to crossing, but not after, commissural axons express robo3 (Rig-1) in addition to robo1 and robo2. The Rig-1 protein inactivates the Robo receptors, preventing the axons from responding to the repellent effects of Slits as they approach the ventral midline.

D. After commissural axons cross the midline, Wnt proteins secreted from floor plate cells and distributed in a rostrocaudal gradient interact with frizzled (**Fz**) proteins on the commissural axons, guiding the axons toward the brain.

of the spinal cord. In addition, activated Robo forms a complex with DCC, rendering these Netrin receptors incapable of responding to their ligand. The decreased sensitivity of growth cones to the attractive properties of the floor plate helps to account for the transient influence of floor plate signals on axons.

Finally, once axons have left the floor plate, they turn rostrally toward their eventual synaptic targets in the brain. A rostrocaudal gradient of Wnt proteins expressed by floor plate cells appears to direct axon growth rostrally at the ventral midline (Figure 47–18D). Thus, different cues guide commissural axons during distinct phases of their overall trajectory. This same process is presumably played out for hundreds and even thousands of classes of neurons to establish the mature pattern of brain wiring.

Highlights

1. As neurons extend processes, one generally becomes an axon and the others become dendrites. This process is called polarization. The two types of processes differ in structure and molecular architecture as well as function.
2. Cell types differ markedly in the shape, size, and branching patterns of their dendrites. Type-specific dendritic features arise both from intrinsic differences in transcriptional programs among types and from extrinsic influences on the developing dendrites.
3. Interactions among dendrites are critical for dendritic patterning. Repellent interactions among the dendrites of a single cell, a process called self-avoidance, leads to even coverage of an area, with minimal gaps or clumps. Repellent actions between dendrites of neighboring cells, a process called tiling, minimizes overlap of dendritic fields. In some cases, dendrites avoid other dendrites from their own neuron but interact with dendrites of nominally identical neighboring cells. This process is called self-/non–self-discrimination.
4. Growth cones at the tips of axons serve as both sensory and motor elements to guide axons to their destinations. Cytoskeletal elements of the growth cone, including actin and myosin, propel the growth.
5. Receptors on the growth cone recognize and bind ligands in the environment through which the axon is extending, guiding the growth. These interactions lead to generation of their second messengers that mediate growth, turning and stopping of the growth cone, and branching of the axon.
6. Some growth cones contain protein synthetic machinery including messenger RNAs. In these cases, receptors can promote local synthesis of specific proteins that mediate growth or turning.
7. Ligand–receptor pairs include several key families of molecules including cadherins, Slits and their Robo receptors, semaphorins and their plexin receptors, and ephrins and their Eph kinase receptors.
8. The growth of an axon to a distant target is broken into discrete shorter steps. At each step, molecules on the surface of or secreted by neighboring structures guide the axon. They can also lead to alterations in the growth cone's complement of receptors, allowing it to respond to different sets of cues at the subsequent stage.
9. Roger Sperry proposed a chemospecificity hypothesis to explain the specific growth of axons from different parts of the retina to different parts of the optic tectum (superior colliculus), forming an orderly retinotopic map. The ephrins and their receptors, the Eph kinases, are key molecules that guide map formation. They are graded in expression along the retina and tectum and act in large part by repelling axons from incorrect positions rather than attracting them to correct positions.
10. Both attractive and repellent molecules guide axons across midline structures, a process called decussation. Evolutionarily conserved signals include Slits, netrins, and Wnts. Mutations in genes that encode these ligands and receptors can result in developmental neurological disorders.

Joshua R. Sanes

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