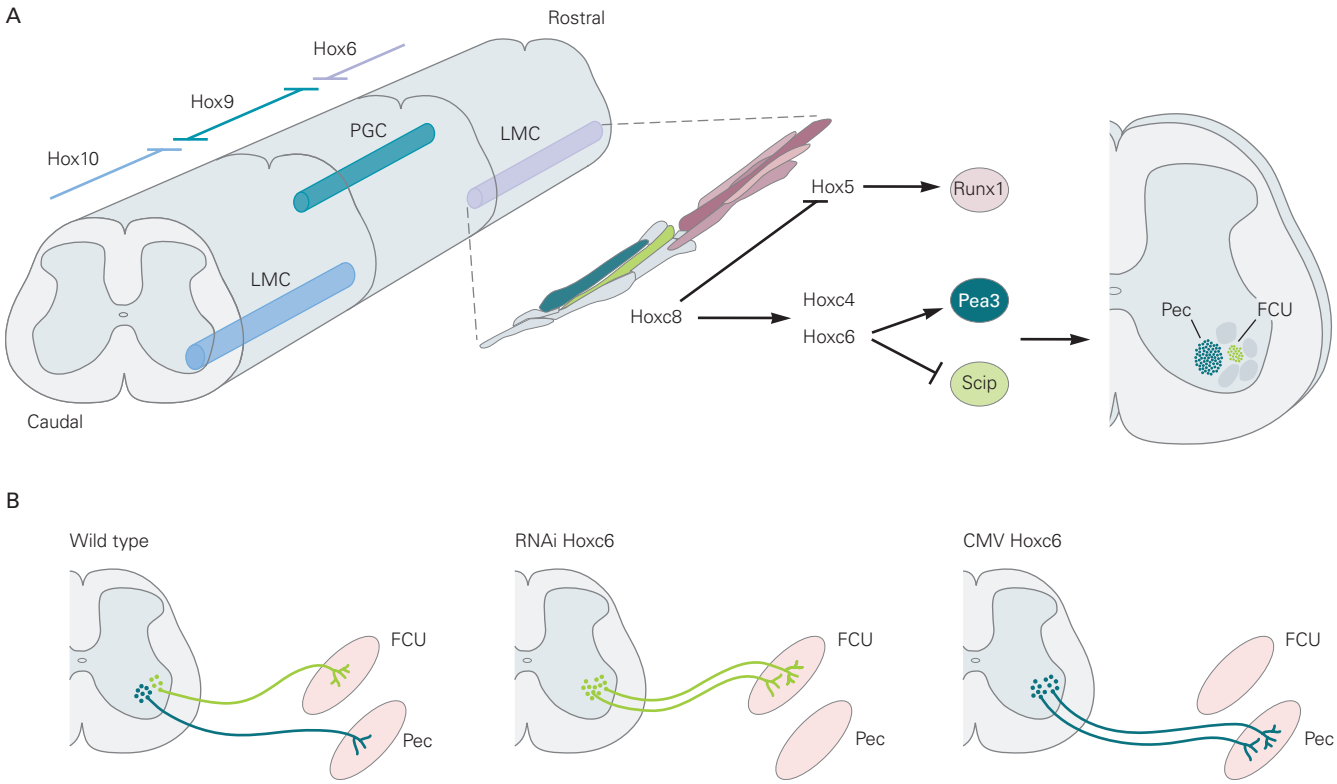

Figure 45–13 Hox proteins control the identity of neurons in motor columns and pools. (Adapted, with permission, from Dasen et al. 2005.)

A. Hox6, Hox9, and Hox10 proteins are expressed in motor neurons at distinct rostrocaudal levels of the spinal cord and direct motor neuron identity and peripheral target connectivity. Hox6 activities control the identity of cells in the brachial lateral motor column (**LMC**), Hox9 controls the identity of cells in the preganglionic column (**PGC**), and Hox10 controls the identity of cells in the lumbar column (**LMC**). Cross-repressive interactions between Hox6, Hox9, and Hox10 proteins refine Hox profiles, and Hox activator functions define LMC and PGC identities. A more complex Hox transcriptional network controls motor pool identity and connectivity. Hox genes determine the rostrocaudal position of motor pools within the LMC. Hoxc8 is required in caudal LMC neurons to generate the motor pools for the pectoralis (**Pec**) and flexor carpi ulnaris (**FCU**) muscles; these neurons express the transcription factors Pea3 and Scip, respectively. The patterns of Hox expression in the Pec and FCU pools are established through a transcriptional network that appears to be driven largely by Hox cross-repressive interactions.

B. Changing the Hox code within motor pools changes the pattern of muscle connectivity. Alterations in the profile of Hox6 expression determine the expression of Pea3 and Scip and control the projection of motor axons to the Pec or FCU muscles. RNA interference (**RNAi**) knock-down of Hox6 suppresses innervation of the Pec muscle so that motor axons innervate the FCU muscle only. Ectopic expression of Hoxc6 driven by a cytomegalovirus (**CMV**) promoter represses connectivity with FCU, so that motor axons innervate only the Pec muscle.

The spatial distribution of Pax6 and Emx2 helps to establish the initial regional pattern of the neocortex. In mice lacking Emx2 activity, there is an expansion of rostral neocortex—the motor and somatosensory areas—at the expense of the more caudal auditory and visual areas. Conversely, in mice lacking Pax6 activity, visual and auditory areas are expanded at the expense of motor and somatosensory areas (Figure 45–15B).

Thus, as in the spinal cord, hindbrain, and midbrain, early neocortical patterns are established through the interplay between local inductive signals and gradients of transcription factor expression. How these gradients specify discrete functional areas in the neocortex remains unclear. Unlike segmentation in the hindbrain, where transcription factors precisely specify rhombomeres, transcriptional markers of individual neocortical areas have not yet been identified.

Afferent Inputs Also Contribute to Regionalization

In the adult neocortex, different functional areas can be distinguished by differences in the layering pattern of neurons—the cytoarchitecture of the areas—and by their neuronal connections. One striking instance of

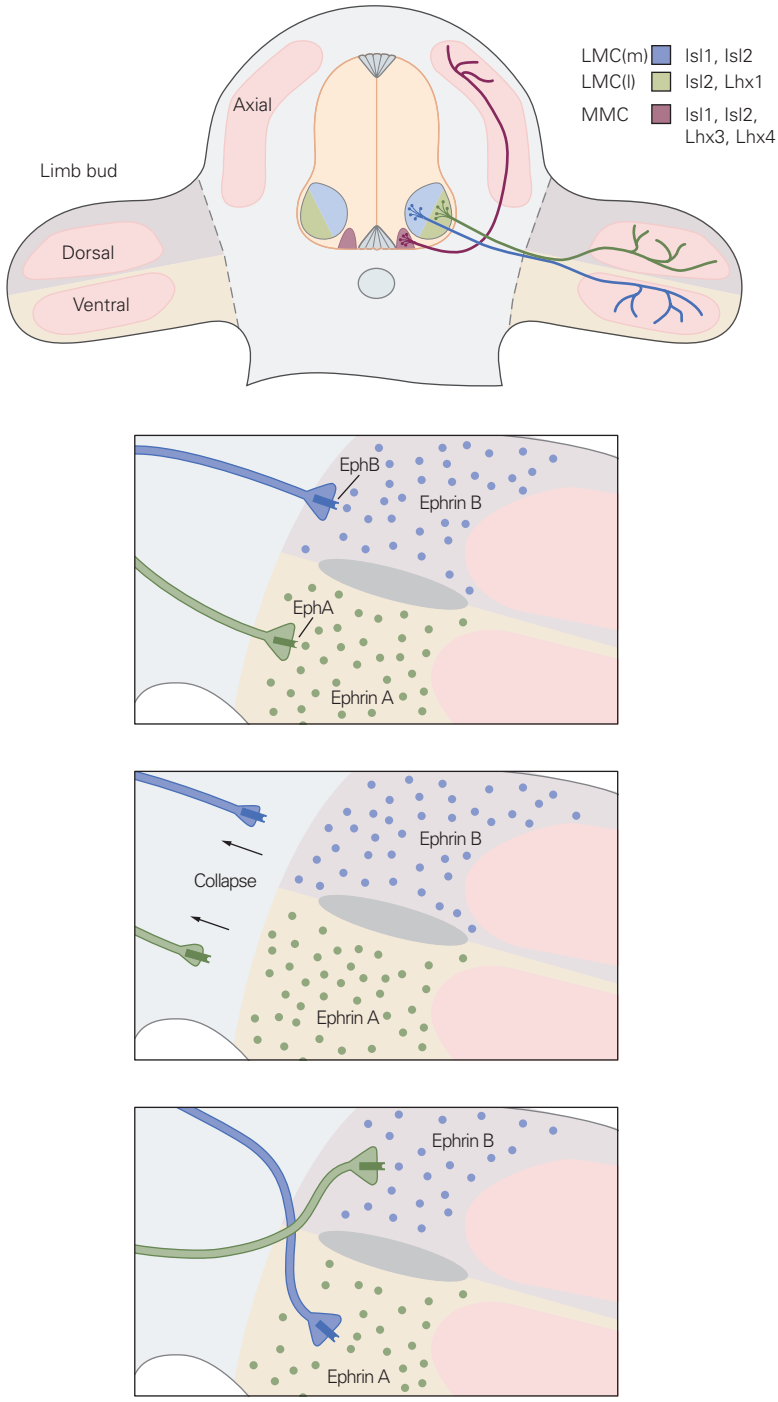

Figure 45–14 **The axons of lateral motor column neurons are guided into the limb by ephrin class tyrosine kinase receptors.** Motor neurons in the medial and lateral divisions of the lateral motor column (**LMC**) project axons into the ventral and dorsal halves of the limb mesenchyme, respectively. The profile of expression of LIM class homeodomain proteins regulates this dorsoventral projection. The LIM homeodomain protein Isl1 expressed by medial LMC neurons directs a high level of expression of EphB receptors, such that as the axons of these cells enter the limb, they are prevented from projecting dorsally by the high level of repellant ephrin B ligands expressed by cells of the dorsal limb mesenchyme. These axons therefore project into the ventral limb mesenchyme. Conversely, the LIM homeodomain protein Lhx1 expressed by lateral LMC neurons directs a high level of expression of EphA receptors, such that as the axons of these cells enter the limb, they are prevented from projecting ventrally by the high level of repellant ephrin A ligands expressed by cells of the ventral limb mesenchyme. These axons therefore project into the dorsal limb mesenchyme. Eph and ephrin signaling is discussed in greater detail in Chapter 47. (Abbreviation: **MMC**, medial motor column.)

regional distinctiveness in cell pattern is a grid-like array of neurons and glial cells termed "barrels" in the primary somatosensory cortex of rodents. Each cortical barrel receives somatosensory information from a single whisker on the snout, and the regular array of cortical barrels reflects the somatotopic organization of afferent information from the body surface, culminating in the projection of thalamic efferents to specific cortical barrels (Figure 45–16A).

Cortical barrels are evident soon after birth, and their development depends on a critical period of afferent input from the periphery; their formation is disrupted if the whisker field in the skin is eliminated during this critical period. Strikingly, if prospective

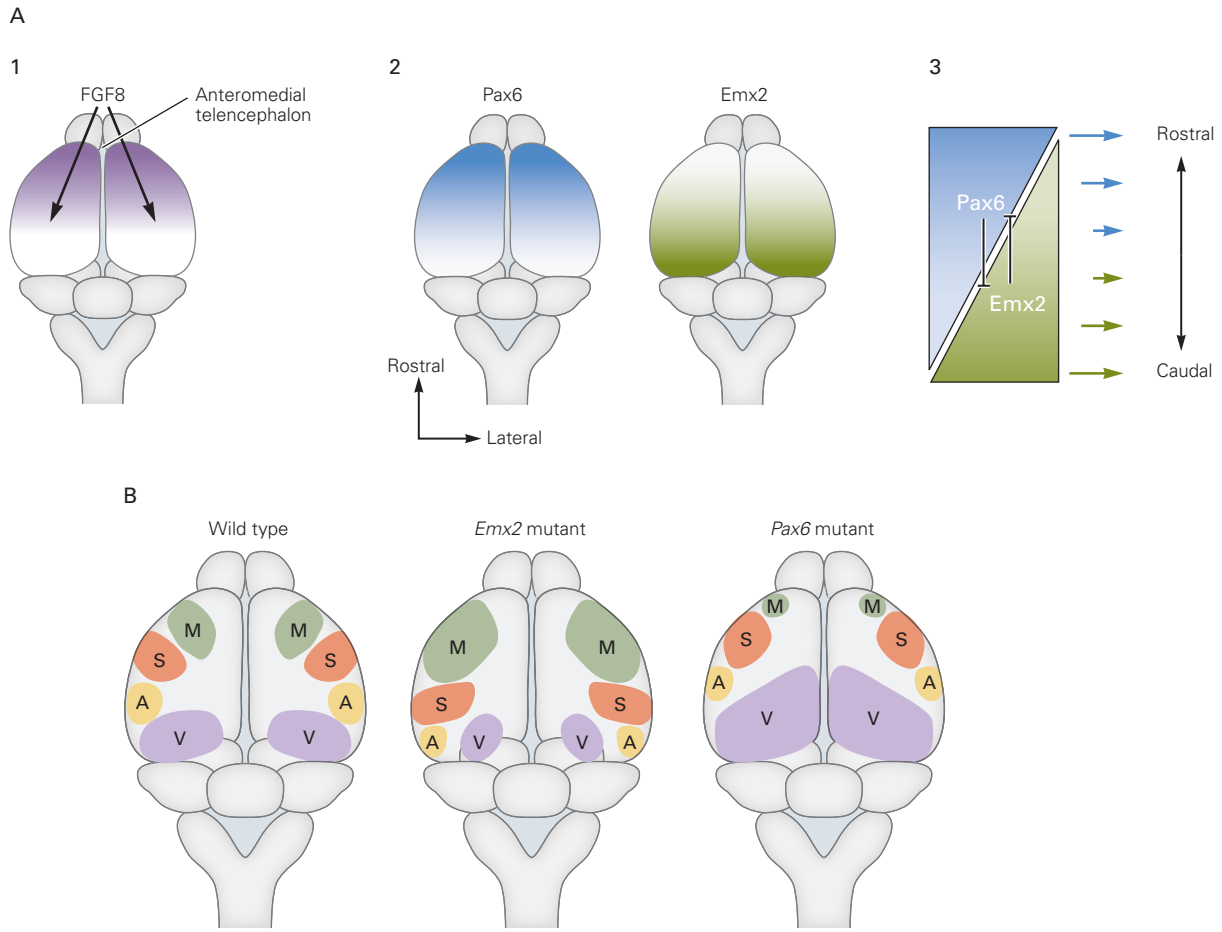

Figure 45–15 Anteroposterior gradients of expression of transcription factors establish discrete functional areas along the anteroposterior axis of the developing forebrain. (Adapted from Hamasaki et al. 2004.)

A. (**1**) FGF8 signals from the anteromedial telencephalon establish the rostrocaudal pattern of the cerebral cortex. (**2**) A top-down view of the developing cerebral cortex in the mouse shows inverse rostrocaudal gradients of the transcription factors Pax6 and Emx2. (**3**) These two transcription factors mutually repress each other's expression.

B. Different functional areas develop at different rostrocaudal positions. Motor areas develop in the anterior region (**M**) and visual areas in more posterior regions (**V**). Genetic elimination of Emx2 function results in expansion of the motor areas and contraction in auditory (**A**) and visual areas. Conversely, elimination of Pax6 function results in an expansion of the visual areas and a contraction of motor and auditory areas. (Abbreviation: **S**, somatosensory areas.)

visual cortical tissue is transplanted into the somatosensory cortex around the time of birth, barrels form in the transplanted tissue with a pattern that closely resembles that of the normal somatosensory barrel field (Figure 45–16B). Together, these findings demonstrate that afferent input superimposes aspects of neocortical patterning on the basic features of the protomap.

The nature of the input to different cortical areas influences neural function as well as cytoarchitecture. This can be shown by monitoring physiological and behavioral responses after rerouting afferent pathways of one sensory modality to a region of neocortex that normally processes a different modality. In animals in which retinal inputs are rerouted into the auditory pathway, the primary auditory cortex contains a systematic representation of visual space rather than of sound frequency (Figure 45–17). When these animals are trained to discriminate a visual from an auditory cue, they perceive a cue as visual when the rewired auditory cortex is activated by vision.

Thus, brain pathways and neocortical regions are established through genetic programs during early development but later depend on afferent inputs for their specialized anatomical, physiological, and behavioral functions.

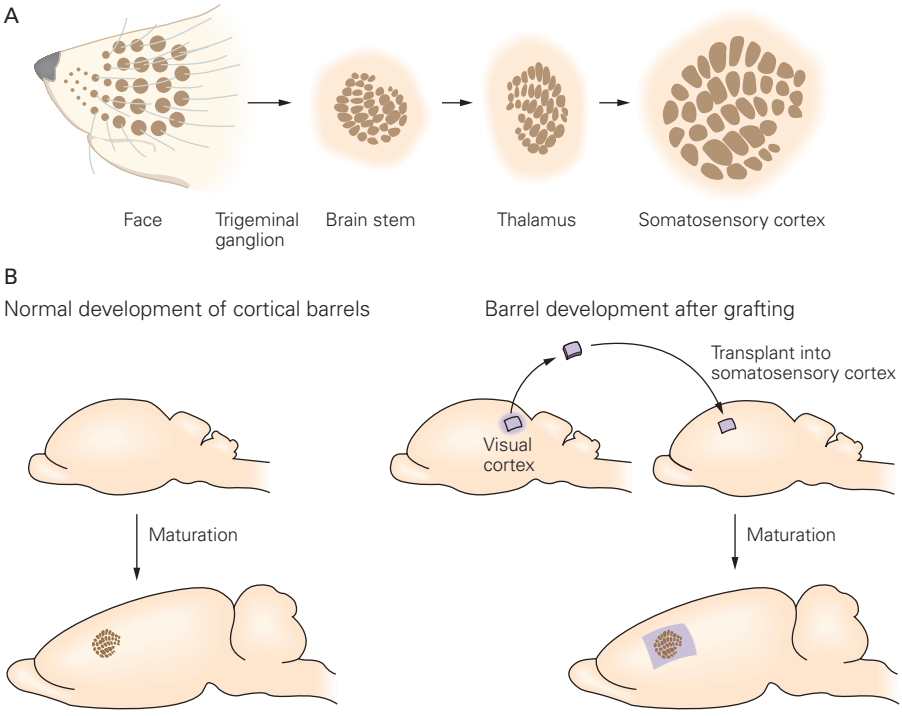

Figure 45–16 Sensory input regulates the organization of "barrels" in the developing somatosensory cortex in rodents. (Adapted from Schlaggar and O'Leary 1991.)

A. The barrel area of the rodent somatosensory cortex forms a somatotopic representation of the rows of whiskers on the animal's snout. Similar representations of the whisker field are present upstream—in the brain stem and in the thalamic nuclei that relay somatosensory inputs from the face to the cortex.

B. A barrel-like cellular organization is induced in developing visual cortex tissue that was grafted at an early postnatal stage into the somatosensory cortex.

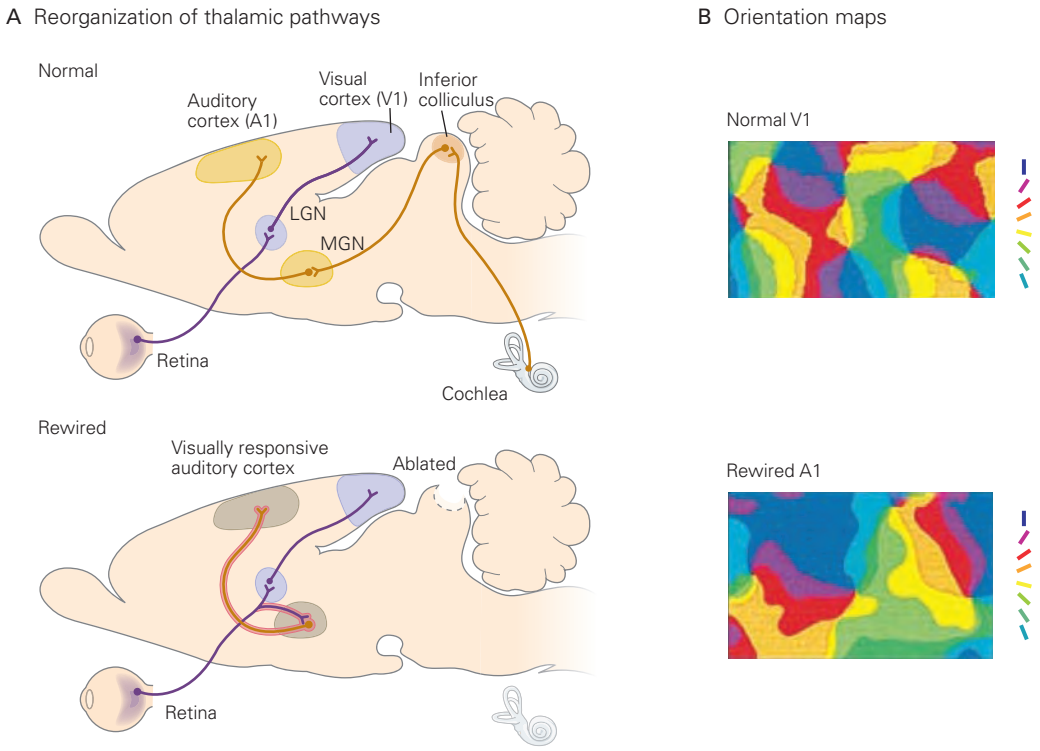

Figure 45–17 Rerouting thalamocortical input can recruit cortical areas for new sensory functions. (Adapted, with permission, from Sharma, Angelucci, and Sur 2000. Copyright © 2000 Springer Nature.)

A. The visual pathway consists of afferent fibers from the retina that innervate the lateral geniculate nucleus (**LGN**) and superior colliculus. Axons from the LGN project to the primary visual cortex (**V1**). The auditory pathway projects from the cochlear nucleus (not shown) to the inferior colliculus, and then to the medial geniculate nucleus (**MGN**) and on to the primary auditory cortex (**A1**). Ablating the inferior colliculus in neonatal ferrets causes retinal afferents to innervate the MGN. As a consequence, the auditory cortex is reprogrammed to process visual information.

B. Visual orientation maps similar to those seen in normal V1 cortex are observed in rewired A1 auditory cortex of ferrets using optical imaging of intrinsic signals. The different colors represent different receptor field orientations (see bars at right). The pattern of activity in rewired A1 resembles that of normal V1.

Highlights

1. The early vertebrate embryo consists of three layers of cells—ectoderm, mesoderm, and endoderm. The entire nervous system arises from the ectoderm, and more specifically from a central strip of ectoderm called the neural plate.
2. Formation of neural plate within the ectoderm occurs by a process called induction, in which underlying mesodermal cells secrete soluble factors that induce a neural program of gene expression in neighboring ectodermal cells. Induction involves a "de-repression" mechanism in which mesoderm-derived soluble factors prevent ectoderm-derived bone morphogenetic proteins (BMPs; members of the transforming growth factor β family) from suppressing the neural fate.
3. Following induction, the neural plate invaginates from the ectoderm to form a neural tube. The tube gives rise to the central nervous system, while cells at the border between neural tube and ectoderm form neural crest, which migrates through the embryo to form the sensory and autonomic ganglia of the peripheral nervous system.
4. As soon as the neural tube forms, it begins to become regionalized. Regionalization along the anterior-posterior axis leads to a series of subdivisions. The anterior region becomes the brain, and the posterior region becomes the spinal cord. Divisions of the prospective brain generate the forebrain, midbrain, and hindbrain. The forebrain divides further to form the telencephalon, from which cortex, hippocampus, and basal ganglia arise; and the diencephalon, which gives rise to thalamus, hypothalamus, and retina. The hindbrain divides to form the pons and cerebellum anteriorly and the medulla posteriorly.
5. Anterior-posterior patterning is established by gradients of Wnt signaling, which arise from selective production of Wnts posteriorly and selective production of Wnt inhibitors anteriorly.
6. Subdivisions along the anteroposterior axis are established by groups of cells called organizing centers at defined positions within the neural tube. The organizing centers secrete factors that pattern neighboring regions of the neural tube and specify neuronal types within them. For example, the isthmic organizer at the boundary of the hindbrain and midbrain secretes Wnts and fibroblast growth factors (FGFs). They act differentially in anterior and posterior regions because the earlier patterning events led to expression of different transcription factors by cells in these regions.
7. Still later, further subdivisions form segments called prosomeres in the forebrain and rhombomeres in the hindbrain, with differential expression of transcription factors leading to generation of distinct neural types in each.
8. In both the hindbrain and the spinal cord, motor neurons acquire distinct properties according to their anterior-posterior position, differentiating into the groups that innervate distinct muscles. Differential expression of transcription factors called Hox proteins is particularly important in diversification of motor neurons. They act with other transcription and soluble factors to divide motor neurons into columns and pools, with each pool destined to innervate a specific muscle.
9. The neural tube is also patterned along the dorsoventral axis. Similar to anterior-posterior regionalization, patterning results from gradients of morphogens. The most important are sonic hedgehog (Shh), which forms a ventral high–dorsal low gradient, and BMPs, which form a dorsal high–ventral low gradient. Different levels of Shh and BMPs induce different transcription factors, which in turn lead to generation of different cell types.
10. Regionalization of the cerebral cortex into motor, sensory, and association areas also begins with gradients of morphogens that induce differential expression of transcription factors, leading to establishment of a "protomap" of area identity. Interactions among areas along with input from subcortical regions refine the protomap to form definitive cortical areas.
11. Several general principles explain many aspects of early neural development: (a) Inductive interactions lead to subdivision of a uniform set of cells into discrete areas. (b) A small set of soluble factors such as FGFs, BMPs, and Wnts are used multiple times at multiple stages to regionalize the nervous system. (c) Varying levels of these factors lead to expression of different transcription factors, which in turn generate different neural cell types. (d) Repressive interactions between cells expressing different transcription factors sharpen boundaries along both anteroposterior and dorsoventral axes.
12. Until recently, studies on early stages of neural development have been restricted to experimental animals. Recent advances now enable neuroscientists to recapitulate some of these processes using cultured human cells. It should therefore

soon be possible to learn whether there are critical early differences between humans and other species that contribute to the complexity of the human brain and to human brain disorders.

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46

Differentiation and Survival of Nerve Cells

The Proliferation of Neural Progenitor Cells Involves Symmetric and Asymmetric Cell Divisions

Radial Glial Cells Serve as Neural Progenitors and Structural Scaffolds

The Generation of Neurons and Glial Cells Is Regulated by Delta-Notch Signaling and Basic Helix-Loop-Helix Transcription Factors

The Layers of the Cerebral Cortex Are Established by Sequential Addition of Newborn Neurons

Neurons Migrate Long Distances From Their Site of Origin to Their Final Position

- Excitatory Cortical Neurons Migrate Radially Along Glial Guides
- Cortical Interneurons Arise Subcortically and Migrate Tangentially to Cortex
- Neural Crest Cell Migration in the Peripheral Nervous System Does Not Rely on Scaffolding

Structural and Molecular Innovations Underlie the Expansion of the Human Cerebral Cortex

Intrinsic Programs and Extrinsic Factors Determine the Neurotransmitter Phenotypes of Neurons

- Neurotransmitter Choice Is a Core Component of Transcriptional Programs of Neuronal Differentiation
- Signals From Synaptic Inputs and Targets Can Influence the Transmitter Phenotypes of Neurons

The Survival of a Neuron Is Regulated by Neurotrophic Signals From the Neuron's Target

- The Neurotrophic Factor Hypothesis Was Confirmed by the Discovery of Nerve Growth Factor
- Neurotrophins Are the Best-Studied Neurotrophic Factors
- Neurotrophic Factors Suppress a Latent Cell Death Program

Highlights

In the preceding chapter, we described how local inductive signals pattern the neural tube and establish the early regional subdivisions of the nervous system—the spinal cord, hindbrain, midbrain, and forebrain. Here, we turn to the issue of how progenitor cells within these regions differentiate into neurons and glial cells, the two major cell types of the nervous system. The mature brain comprises billions of nerve cells and a similar number of glial cells arranged in complex patterns, yet its precursor, the neural plate, initially contains only a few hundred cells arranged in a simple columnar epithelium. From this observation alone, it should be apparent that the generation of neural cells and their delivery to appropriate sites must be carefully regulated.

We begin by discussing some of the molecules that specify neuronal and glial cell fates. The basic mechanisms of neurogenesis endow cells with common neuronal properties, features that are largely independent of the region of the nervous system in which they are generated or the specific functions they perform. We also describe mechanisms by which developing neurons become specialized, for example by acquiring the machinery to synthesize specific neurotransmitters.

We next discuss how neurons are delivered from their sites of origin to their final destinations. A common theme is that neurons are frequently "born"—that is, become postmitotic—far from where they end up, for example, in the layers of the cerebral cortex or the ganglia of the peripheral nervous system. Such distances necessitate elaborate migratory mechanisms, which differ among neuronal types.

After the identity and functional properties of the neuron have begun to emerge, additional

developmental processes determine whether the neuron will live or die. Remarkably, approximately half of the neurons generated in the mammalian nervous system are lost through programmed cell death. We examine the factors that regulate the survival of neurons and the possible benefits of widespread neuronal loss. Finally, we describe a core biochemical pathway in nerve cells destined for elimination.

The Proliferation of Neural Progenitor Cells Involves Symmetric and Asymmetric Cell Divisions

Histologists in the late 19th century showed that neural epithelial cells close to the ventricular lumen of the embryonic brain exhibit features of mitosis. We now know that the proliferative zones surrounding the ventricles are the major sites for the production of neural cells in the central nervous system. Moreover, newborn cells in the proliferative zones often become committed to neuronal or glial fates before migrating from these zones.

At early stages of embryonic development, most progenitor cells in the ventricular zone of the neural tube proliferate rapidly. Many of these early neural progenitors have the properties of stem cells: They can generate additional copies of themselves, a process called *self-renewal*, and also give rise to differentiated neurons and glial cells. In a later chapter, we will describe the more recent discovery that stem cells resembling those of embryos also exist in the adult brain and may be harnessed for therapeutic purposes (Chapter 50).

As with other types of stem cells, neural progenitor cells undergo stereotyped programs of cell division. One mode of cell division is symmetric: Neural stem cells divide to produce two stem cells, and in this way expand the population of proliferative progenitor cells. This mode predominates at the earliest times, as the neuroepithelium expands. A second mode is asymmetric: The progenitor produces one differentiated daughter and another daughter that retains its stem cell–like properties. This mode retains but does not amplify the stem cell population. A third mode leads to production of two differentiated daughters. In this symmetric mode, the stem cell population is depleted. All three modes have been found in the embryonic cerebral cortex in vivo and in cortical cells grown in tissue culture (Figure 46–1).

The incidence of symmetric and asymmetric cell division is influenced by signals in the local environment of the dividing cell, making it possible to control the probability of self-renewal or differentiation. Environmental factors can influence the outcome of progenitor cell divisions in two fundamental ways. They can act in an "instructive" manner, biasing the outcome of the division process and causing the stem cell to adopt one fate at the expense of others. Or they can act in a "selective" manner, permitting the survival and maturation of only certain cell progeny.

Radial Glial Cells Serve as Neural Progenitors and Structural Scaffolds

Radial glial cells are the earliest morphologically distinguishable cell type to appear within the primitive neural epithelium. Their cell bodies are located in the ventricular zone, and their long process extends to the pial surface. As the brain thickens, the processes of radial glial cells remain attached to the ventricular and pial surfaces. After the generation of neurons is complete, many radial glial cells differentiate into astrocytes. The elongated shape of the radial glial cell places it in a favorable position to serve as a scaffold for the migration of neurons that emerge from the ventricular zone (Figure 46–2).

The ventricular zone was once thought to contain two major cell types: radial glial cells and a set of neuroepithelial progenitors that serve as the primary source of neurons. More recently, this classical view has changed dramatically. Once symmetric divisions of stem cells have expanded the neuroepithelium, these cells give rise to radial glial cells. The radial glial cells serve as progenitor cells that generate both neurons and astrocytes in addition to their role in neuronal migration (Figure 46–2). Labeling of radial glial cells with fluorescent dyes or viruses shows that their clonal progeny include both neuronal and radial glial cells. These findings indicate that radial glial cells are able to undergo both asymmetric and self-renewing cell division and serve as a major source of postmitotic neurons as well as astrocytes.

The Generation of Neurons and Glial Cells Is Regulated by Delta-Notch Signaling and Basic Helix-Loop-Helix Transcription Factors

How do radial glial cells make the decision to self-renew, generate neurons, or give rise to mature astrocytes? The answer to this question involves an evolutionarily conserved signaling system.

In flies and vertebrates, neural fate is regulated by a cell-surface signaling system, comprised of the

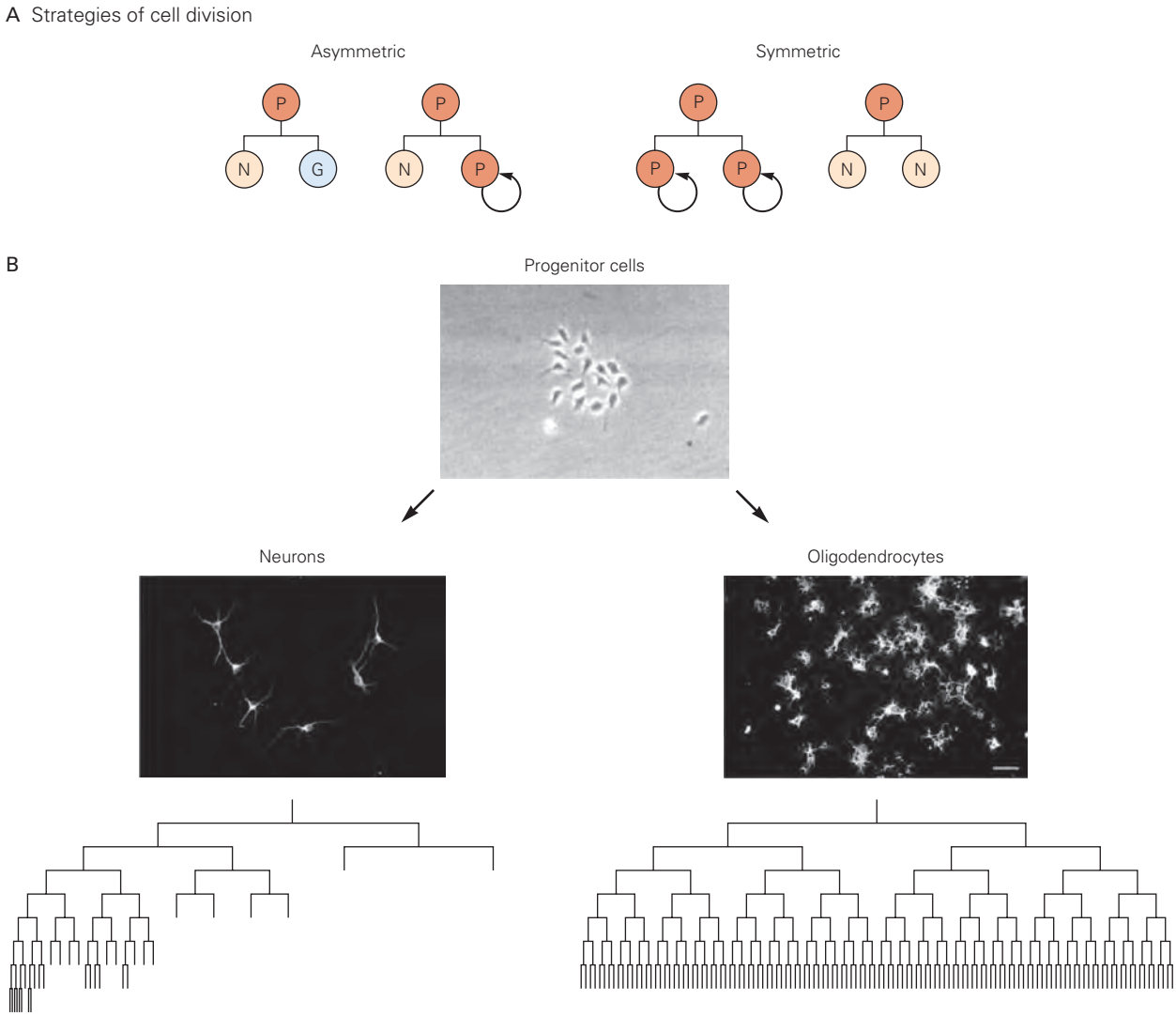

Figure 46–1 Neural progenitor cells have different modes of division.

A. Asymmetric and symmetric modes of cell division. A progenitor cell (P) can undergo asymmetric division to generate a neuron (N) and a glial cell (G), or a neuron and another progenitor. This mode of division contributes to the generation of neurons at early stages of development and of glial cells at later stages, typical of many regions of the central nervous system. Progenitor cells can also undergo symmetric division to generate two additional progenitor cells or two postmitotic neurons.

B. Time-lapse cinematography captures the divisions and differentiation of isolated cortical progenitor cells in the rodent. Lineage diagrams illustrate cells that undergo predominantly asymmetric division, giving rise to neurons, or symmetric division, giving rise to oligodendrocytes. (Adapted, with permission, from Qian et al. 1998. Permission conveyed through Copyright Clearance Center, Inc.)

transmembrane ligand Delta and its receptor Notch. This signaling system was revealed in genetic studies in *Drosophila*. Neurons emerge from within a larger cluster of ectodermal cells, called a *proneural region*, all of which have the potential to generate neurons. Yet within the proneural region, only certain cells form neurons; the others become epidermal support cells.

Delta and Notch are initially expressed at similar levels by all proneural cells (Figure 46–3A). With time, however, Notch activity is enhanced in one cell and suppressed in its neighbor. The cell in which Notch activity is highest loses the potential to form a neuron and acquires an alternative fate. The binding of Delta to Notch results in proteolytic cleavage of the Notch cytoplasmic domain, which then enters the nucleus.