the strategies and principles that establish dorsoventral pattern. We focus initially on the mechanisms of dorsoventral patterning at caudal levels of the neural tube that give rise to the spinal cord and then describe how similar strategies are used to pattern the forebrain.

Neurons in the spinal cord serve two major functions. They relay cutaneous sensory input to higher centers in the brain, and they transform sensory input into motor output. The neuronal circuits that mediate these functions are segregated anatomically. Circuits involved in the processing of cutaneous sensory information are located in the dorsal half of the spinal cord, whereas those involved in the control of motor output are mainly located in the ventral half of the spinal cord.

The neurons that form these circuits are generated at different positions along the dorsoventral axis of the spinal cord in a patterning process that begins with the establishment of distinct progenitor cell types. Motor neurons are generated close to the ventral midline, and most of the interneuron classes that control motor output are generated just dorsal to the position at which motor neurons appear (Figure 45–8). The dorsal half of the neural tube generates projection neurons and local circuit interneurons that process incoming sensory information.

How are the position and identity of spinal neurons established? The dorsoventral patterning of the neural tube is initiated by signals from mesodermal and ectodermal cells that lie close to the ventral and dorsal poles of the neural tube and is perpetuated by signals from two midline neural organizing centers. Ventral patterning signals are initially provided by the notochord, a mesodermal cell group that lies immediately under the ventral neural tube (Figure 45–1). This signaling activity is transferred to the floor plate, a specialized glial cell group that sits at the ventral midline of the neural tube itself. Similarly, dorsal signals are provided initially by cells of the epidermal ectoderm that span the dorsal midline of the neural tube, and subsequently by the roof plate, a glial cell group embedded at the dorsal midline of the neural tube (Figure 45–8).

Thus, neural patterning is initiated through a process of *homogenetic* induction, in which like begets like: Notochord signals induce the floor plate, which

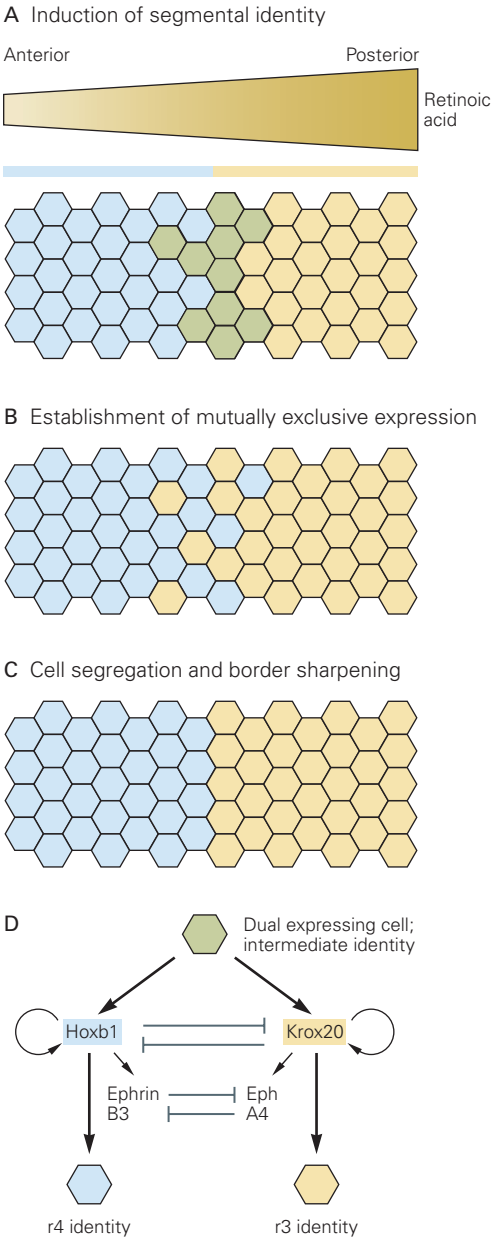

Figure 45–7 (Left) **Repressive interactions divide the hindbrain into rhombomeres.** The sharp border between hindbrain rhombomeres 3 and 4 forms in several steps. (Adapted, with permission, from Addison and Wilkinson 2016. Copyright © 2016 Elsevier Inc.)

A. A gradient of retinoic acid upregulates expression of *hoxb1* in anterior cells (**blue**) and *krox20* in posterior cells (**yellow**), with some cells at the prospective border expressing both genes (**green**).

B. Hoxb1 expression and Krox20 expression become mutually exclusive, thus endowing each cell with a unique molecular identity.

C. Cells trapped in the wrong domain migrate to sharpen the border.

D. Inhibitory interactions underlying border formation. Hoxb1 and Krox20 repress each other's expression in individual cells, so a modest imbalance in level leads to exclusive expression of one factor. Krox20 then upregulates EphA4 in r3 cells, whereas ephrinB3 is upregulated in r4 cells. EphA4 and ephrinB3 repel each other, driving migration of isolated cells and sharpening the segment border.

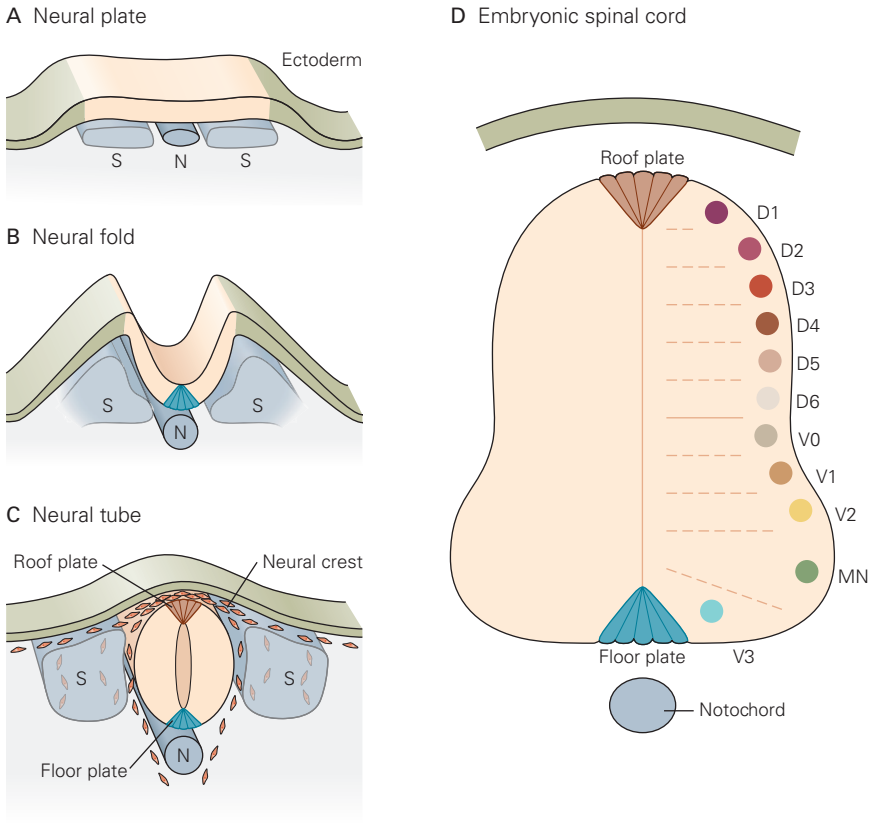

Figure 45–8 Distinct precursor populations form along the dorsoventral axis of the developing spinal cord.

A. The neural plate is generated from ectodermal cells that overlie the notochord (**N**) and the future somites (**S**). It is flanked by the epidermal ectoderm. (See also Figure 45–1)

B. The neural plate folds dorsally at its midline to form the neural fold. Floor plate cells (**blue**) differentiate at the ventral midline of the neural tube.

C. The neural tube forms by fusion of the dorsal tips of the neural folds. Roof plate cells form at the dorsal midline of the neural tube. Neural crest cells migrate from the neural tube into and past the somites before populating the sensory and sympathetic ganglia.

D. Distinct classes of neurons are generated at different dorsoventral positions in the embryonic spinal cord. Ventral interneurons (**V0–V3**) and motor neurons (**MN**) differentiate from progenitor domains in the ventral spinal cord. Six classes of early dorsal interneurons (**D1–D6**) develop in the dorsal half of the spinal cord. (Adapted from Goulding et al. 2002.)

induces ventral neurons, and signals from ectoderm induce the roof plate, which induces dorsal neurons. This strategy ensures that inductive signals are positioned appropriately to control neural cell fate and pattern over a prolonged period of development, as tissues grow and cells move.

The Ventral Neural Tube Is Patterned by Sonic Hedgehog Protein Secreted from the Notochord and Floor Plate

Within the ventral half of the neural tube, the identity and position of developing motor neurons and local interneurons depend on the inductive activity of the Shh protein, which is secreted by the notochord and subsequently by the floor plate. Shh is a member of a family of secreted proteins related to the *Drosophila* hedgehog protein, which had been discovered earlier and shown to control many aspects of embryonic development.

Shh signaling is necessary for the induction of each of the neuronal classes generated in the ventral half of the spinal cord. How can a single inductive signal specify the fate of at least half a dozen neuronal classes? The answer lies in the ability of Shh to act as a morphogen—a signal that can direct different cell fates at different concentration thresholds. The secretion of Shh from the notochord and floor plate establishes a ventral-to-dorsal gradient of Shh protein activity in the ventral neural tube, such that progenitor cells occupying different dorsoventral positions within the neural epithelium are exposed to small (two- to three-fold) differences in ambient Shh signaling activity. Different levels of Shh signaling activity direct progenitor cells in different ventral domains to differentiation as motor neurons and interneurons (Figure 45–9A).

These findings raise two additional questions. How is the spread of Shh protein within the ventral neural epithelium controlled in such a precise manner? And how are small differences in Shh signaling activity converted into all-or-none decisions about the identity of progenitor cells in the ventral neural tube?

Active Shh protein is synthesized from a larger precursor protein, cleaved through an unusual autocatalytic process that involves a serine protease-like activity resident within the carboxy terminus of the precursor protein. Cleavage generates an amino

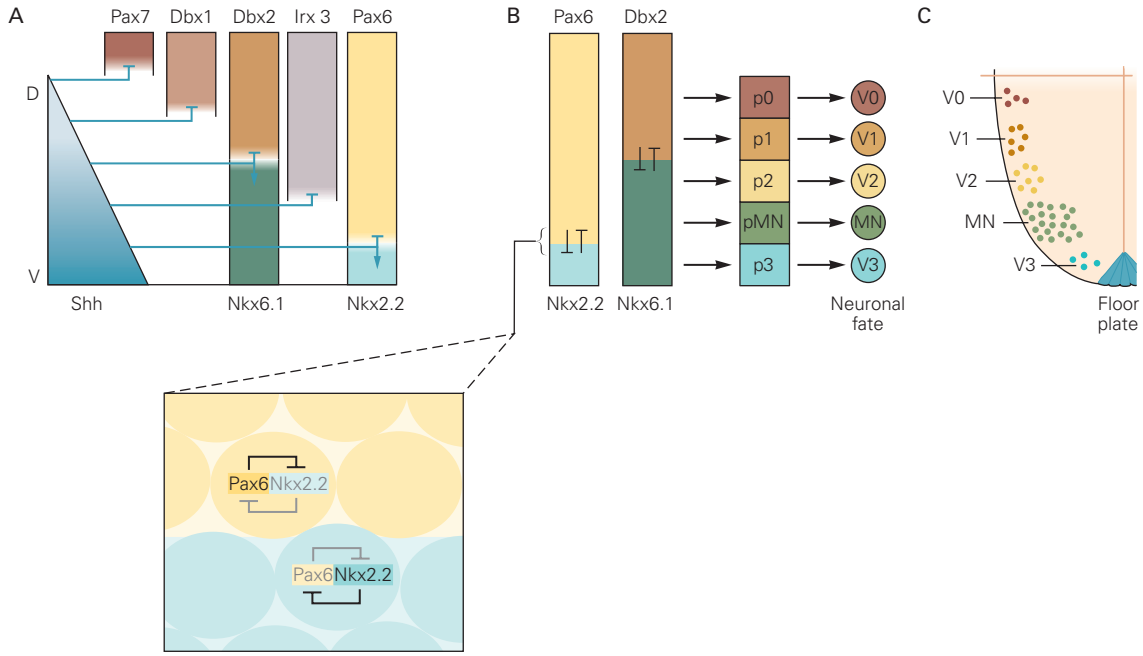

Figure 45–9 A sonic hedgehog signaling gradient controls neuronal identity and pattern in the ventral spinal cord.

A. A ventral-to-dorsal (**V–D**) gradient of sonic hedgehog (**Shh**) signaling establishes dorsoventral domains of homeodomain protein expression in progenitor cells within the ventral half of the neural tube. At each concentration, a different homeodomain transcription factor (Pax7, Dbx1, Dbx2, Irx3, or Pax6) is repressed, with Pax7 the most sensitive and Pax6 the least sensitive to repression. Other homeodomain transcription factors (Nkx6.1 and Nkx2.2) are induced at different Shh levels. The homeodomain proteins that abut a common progenitor domain boundary have similar Shh concentration thresholds for repression and activation. Graded Shh signaling generates a corresponding gradient of Gli transcription factor activity (not shown).

B. Cross-repression between transcription factors induced or repressed by Shh/Gli signaling specifies different neuronal classes. For example, Pax6 and Nkx2.2, and Dbx2 and Nkx6.1, act in a cell-autonomous manner to repress each other's expression (inset), conferring cell identity to progenitor cells in an unambiguous manner. The sequential influence of graded Shh and Gli signaling, together with homeodomain transcriptional cross-repression, establishes five cardinal progenitor domains.

C. The postmitotic neurons that emerge from these domains give rise to the five major classes of ventral neurons: the interneurons **V0–V3** and motor neurons (**MN**).

terminal protein fragment that possesses all of the signaling activity of Shh. During cleavage, the active amino terminal fragment is modified covalently by the addition of a cholesterol molecule. Following Shh secretion, this lipophilic anchor tethers most of the protein to the surface of notochord and floor plate cells. Nevertheless, a small fraction of the anchored protein is released from the cell surface and transferred from cell to cell within the ventral neural epithelium. In reality, the molecular machinery that ensures the formation of a long-distance gradient of extracellular Shh protein is more complex, involving specialized transmembrane proteins that promote the release of Shh from the floor plate, as well as proteins that regulate Shh protein transfer between cells.

How does the gradient of Shh protein within the ventral neural tube direct progenitor cells along different pathways of differentiation? Shh signaling is initiated by its interaction with a transmembrane receptor complex that consists of a ligand-binding subunit called *patched* and a signal-transducing subunit called *smoothened* (named for the corresponding *Drosophila* genes). The binding of Shh to patched relieves its inhibition of smoothened and so activates an intracellular signaling pathway that involves several protein kinase enzymes, transport proteins, and most important, the Gli proteins, a class of zinc finger transcription factors.

In the absence of Shh, the Gli proteins are proteolytically processed into transcriptional repressors that prevent the activation of Shh target genes. Activation of the Shh signaling pathway inhibits this proteolytic processing, with the result that transcriptional activator forms of Gli predominate, thus directing the expression of Shh target genes. In this way, an extracellular gradient of Shh protein is converted into a nuclear gradient of Gli activator proteins. The ratio of

Gli repressor and activator proteins at different dorsoventral positions determines which target genes are activated.

What genes are activated by Shh-Gli signaling, and how do they participate in the specification of ventral neuronal subtypes? The major Gli targets are genes encoding yet more transcription factors. One major class of Gli targets encodes homeodomain proteins, transcription factors that contain a conserved DNA-binding motif termed a *homeobox*. A second major class of target genes encodes proteins with a basic helix-loop-helix DNA-binding motif. Some homeodomain and basic helix-loop-helix proteins are repressed and others activated by Shh signaling, each at a particular concentration threshold. In this way, cells in the ventral neural tube are allocated to one of five cardinal progenitor domains, each marked by its own transcription factor profile (Figure 45–9B,C).

The transcription factors that define adjacent progenitor domains repress each other's expression. Thus, although a cell may initially express several transcription factors that could direct the cell along different pathways of differentiation, a minor imbalance in the starting concentration of the two factors is rapidly amplified through repression, and only one of these proteins is stably expressed. This winner-take-all strategy of transcriptional repression sharpens the boundaries of progenitor domains and ensures that an initial gradient of Shh and Gli activity will resolve itself into clear distinctions in transcription factor profile. The transcription factors that specify a ventral progenitor domain then direct the expression of downstream genes that commit progenitor cells to a particular postmitotic neuronal identity. Thus, studies of Shh signaling have not only revealed the logic of ventral neuronal patterning but also demonstrated that the fate of a neuron is determined in part by the actions of transcriptional repressors rather than activators. This principle operates in many other tissues and organisms.

Although originally studied in the context of neural development, defects in Shh signaling have now been implicated in a wide variety of human diseases. Mutations in human Shh pathway genes result in defects in the development of ventral forebrain structures (holoprosencephaly), as well as neurological defects such as spina bifida, limb deformities, and certain cancers.

The Dorsal Neural Tube Is Patterned by Bone Morphogenetic Proteins

A signaling strategy based on graded morphogen levels activating sets of transcriptional programs has also been found to determine the patterning of cell types in the dorsal spinal cord. The differentiation of roof plate cells at the dorsal midline of the neural tube is triggered by BMP signals from epidermal cells that initially border the neural plate and later flank the dorsal neural tube.

After the neural tube has closed, roof plate cells themselves begin to express BMP as well as Wnt proteins. Wnt proteins promote the proliferation of progenitor cells in the dorsal neural tube. BMP proteins induce the differentiation of neural crest cells at the very dorsal margin of the neural tube and later induce generation of diverse populations of sensory relay neurons that settle in the dorsal spinal cord.

Dorsoventral Patterning Mechanisms Are Conserved Along the Rostrocaudal Extent of the Neural Tube

The strategies used to establish dorsoventral pattern in the spinal cord also control cell identity and pattern along the dorsoventral axis of the hindbrain and midbrain, as well as throughout much of the forebrain.

In the mesencephalic region of the neural tube, Shh signals from the floor plate act in concert with the rostrocaudal patterning signals discussed earlier to specify dopaminergic neurons of the substantia nigra and ventral tegmental area as well as serotonergic neurons of the raphe nuclei (see Figure 45–5C). In the forebrain, Shh signals from the ventral midline and BMP signals from the dorsal midline act in combination to establish different regional domains. Shh signaling from the ventral midline sets up early progenitor domains that later produce neurons of the basal ganglia and some cortical interneurons, whereas BMP signaling from the dorsal midline is involved in establishing early neocortical character.

Local Signals Determine Functional Subclasses of Neurons

To this point, we have seen how a uniform group of neural precursor cells, the neural plate, is progressively partitioned into discrete rostrocaudal and dorsoventral domains within the neural tube, largely by morphogen-dependent differential expression of different sets of transcriptional regulators. The next question is how cells within these domains go on to generate the extraordinary diversity of neuronal types that characterize the vertebrate central nervous system. We address that question by focusing on development of the motor neuron.

Motor neurons can be distinguished from all other classes of neurons in the central nervous system by the simple fact that they have axons that extend into the periphery. Viewed in this light, motor neurons represent a coherent and distinct class. But motor neuron types can be distinguished by their position within the central nervous system as well as by the target cells they innervate. The primary job of most motor neurons is to innervate skeletal muscles, of which there are approximately 600 in a typical mammal. From this, it follows that there must be an equal number of motor neuron types.

In this section, we discuss the developmental mechanisms that direct the differentiation of these different functional subclasses. The details of motor neuron development are also important for understanding the basis of neurological disorders that affect these neurons, including spinal muscular atrophy and amyotrophic lateral sclerosis (Lou Gehrig disease). In both diseases, some motor neuron types are highly vulnerable whereas others are relatively resilient. Similar principles drive the diversification of other neuronal classes into distinct types.

Rostrocaudal Position Is a Major Determinant of Motor Neuron Subtype

Motor neurons are generated along much of the rostrocaudal axis of the neural tube, from the midbrain to the spinal cord. Distinct motor neuron types develop at each rostrocaudal level (Figure 45–10), suggesting that one goal of the patterning signals that establish rostrocaudal positional identity within the neural tube is to make motor neurons different.

One major class of genes involved in specifying motor neuron types is the *Hox* gene family. Their name reflects the fact that they were the first transcription factors found that contain a homeodomain, a DNA binding domain now known to be present in many transcription factors that regulate developmental processes in organisms as diverse as yeast, plants, and mammals. For example, the *Otx* and *Gbx* genes discussed above contain homeodomains. The mammalian *Hox* gene family is especially large, containing 39 genes organized in four chromosomal clusters. These genes derive from an ancestral *Hox* complex that also gave rise to the *HOM-C* gene complex in *Drosophila*, where they were initially discovered and analyzed (Figure 45–11).

Members of the vertebrate *Hox* gene family are expressed in overlapping domains along the rostrocaudal axis of the developing midbrain, hindbrain, and spinal cord. As in *Drosophila*, the position of an individual *Hox* gene within its cluster predicts its rostrocaudal domain of expression within the neural tube. In most but not all cases, *Hox* genes located at more 3′ positions within the chromosomal cluster are expressed in more rostral domains, within the midbrain and hindbrain, whereas genes at more 5′ positions are expressed in progressively more caudal positions within the spinal cord (Figures 45–10 and 45–11). This spatial array of *Hox* gene expression determines many aspects of neuronal diversity.

Genetic studies, mostly in mice, have revealed how *Hox* genes control motor neuron identity in the hindbrain and spinal cord. We saw above that Hox genes contribute to formation of the rhombomeres, the fundamental cellular building blocks of the hindbrain. Later, the same genes help to determine the identity of motor neurons within rhombomeres. For example, *Hoxb1* is expressed at high levels in rhombomere 4, the domain that gives rise to facial motor neurons, but is absent from rhombomere 2, the domain that gives rise to trigeminal motor neurons (Figure 45–10).

In the mouse, mutations that eliminate the activity of *Hoxb1* change the fate of cells in rhombomere 4; there is a switch in the identity and connectivity of the motor neurons that emerge from this domain. In the absence of *Hoxb1* function, cells in rhombomere 4 generate motor neurons that innervate trigeminal rather than facial targets, that is, the motor neuron subtype normally generated within rhombomere 2 (Figure 45–12). Many additional studies have confirmed the general principle that motor neuron identity in the hindbrain is controlled by the spatial distribution of *Hox* gene expression.

The control of spinal motor neuron identity is more complicated. Spinal motor neurons are clustered within longitudinal columns that occupy discrete segmental positions, in register with their peripheral targets. Motor neurons that innervate forelimb and hindlimb muscles are found in the lateral motor columns at cervical and lumbar levels of the spinal cord, respectively. In contrast, motor neurons that innervate sympathetic neuronal targets are found within the preganglionic motor column at thoracic levels of the spinal cord. Within the lateral motor columns, motor neurons that innervate a single limb muscle are clustered together into discrete groups, termed *motor pools*. Because each limb in higher vertebrates contains more than 50 different muscle groups, a corresponding number of motor pools are required.

The identity of motor neurons in the spinal cord is controlled by the coordinate activity of *Hox* genes found at more 5′ positions within the chromosomal *Hox* clusters. For example, the spatial domains of expression and activity of Hox6 and Hox9 proteins establish the identities of motor neurons in the

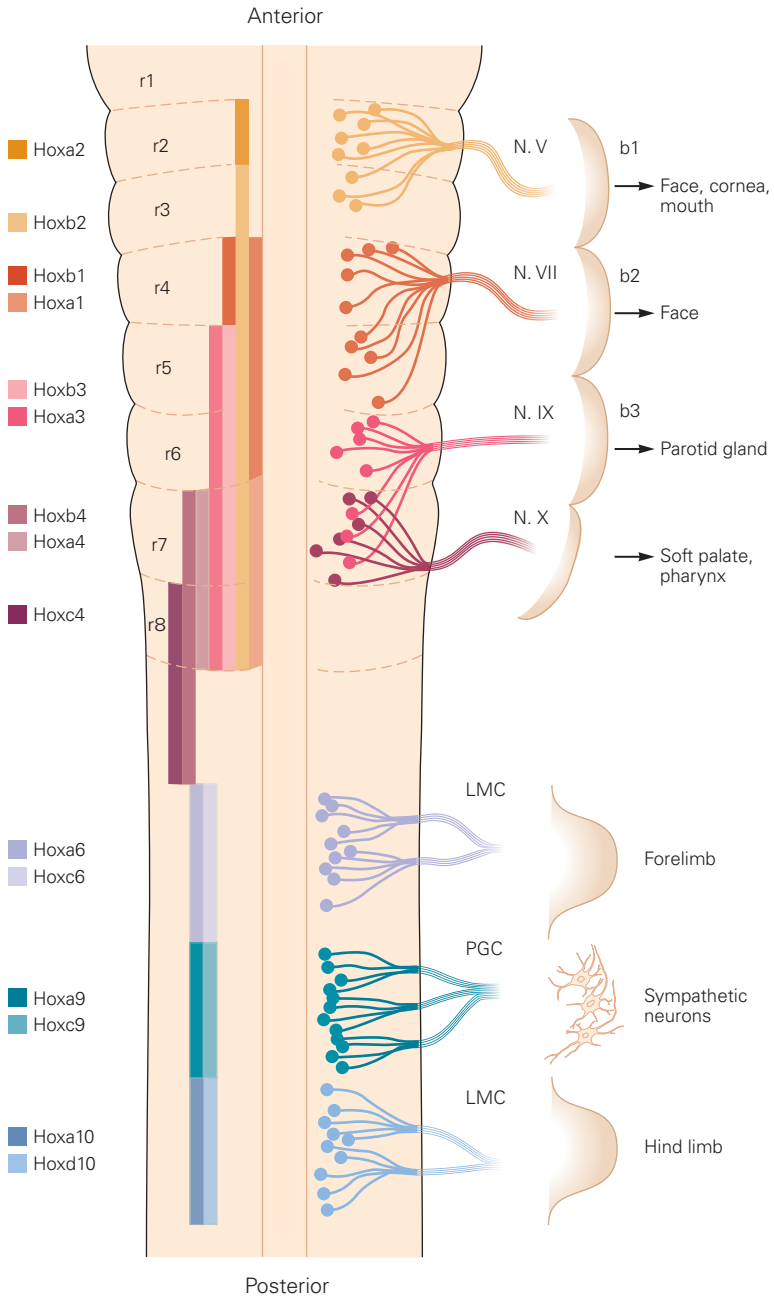

Figure 45–10 The anteroposterior profile of *Hox* gene expression determines the subtype of motor neurons in the hindbrain and spinal cord. Different Hox proteins are expressed in discrete but partially overlapping rostrocaudal domains of the hindbrain and spinal cord. The position of *Hox* genes on the four mammalian chromosomal clusters roughly corresponds to their domain of expression along the anteroposterior axis of the neural tube.

At hindbrain levels, motor neurons sending axons into cranial nerves V (trigeminal), VII (facial), IX (glossopharyngeal), and X (vagus) are depicted. These cranial motor nerves project to peripheral targets in the branchial arches **b1–b3**. The hindbrain rhombomeres (**r1–r8**) and Hox profiles are shown on the left.

At spinal levels, motor neurons that send axons to the forelimb and hind limb are contained within the lateral motor columns (**LMC**), located at brachial and lumbar levels of the spinal cord, respectively. Preganglionic autonomic motor neurons (**PGC**) destined to innervate sympathetic ganglion targets are generated at thoracic levels. (Adapted, with permission, from Kiecker and Lumsden 2005. Copyright © 2005 Springer Nature.)

brachial lateral motor column and the preganglionic motor column. Hox6 proteins specify brachial lateral motor column identity, whereas Hox9 proteins specify preganglionic motor column identity. Motor neurons at the boundary of the forelimb and thoracic regions acquire an unambiguous columnar identity because the Hox6 and Hox9 proteins are mutually repressive (Figure 45–13A), similar to the transcriptional cross-repression that occurs in the dorsoventral patterning of the spinal cord.

Local Signals and Transcriptional Circuits Further Diversify Motor Neuron Subtypes

How do motor neurons within the lateral motor columns develop more refined identities, directing their axons to specific limb muscles? Once again, *Hox* genes control this stage of motor neuron diversification. We illustrate this function of Hox proteins by considering the pathway that generates the distinct divisional and pool identities of neurons within the brachial lateral

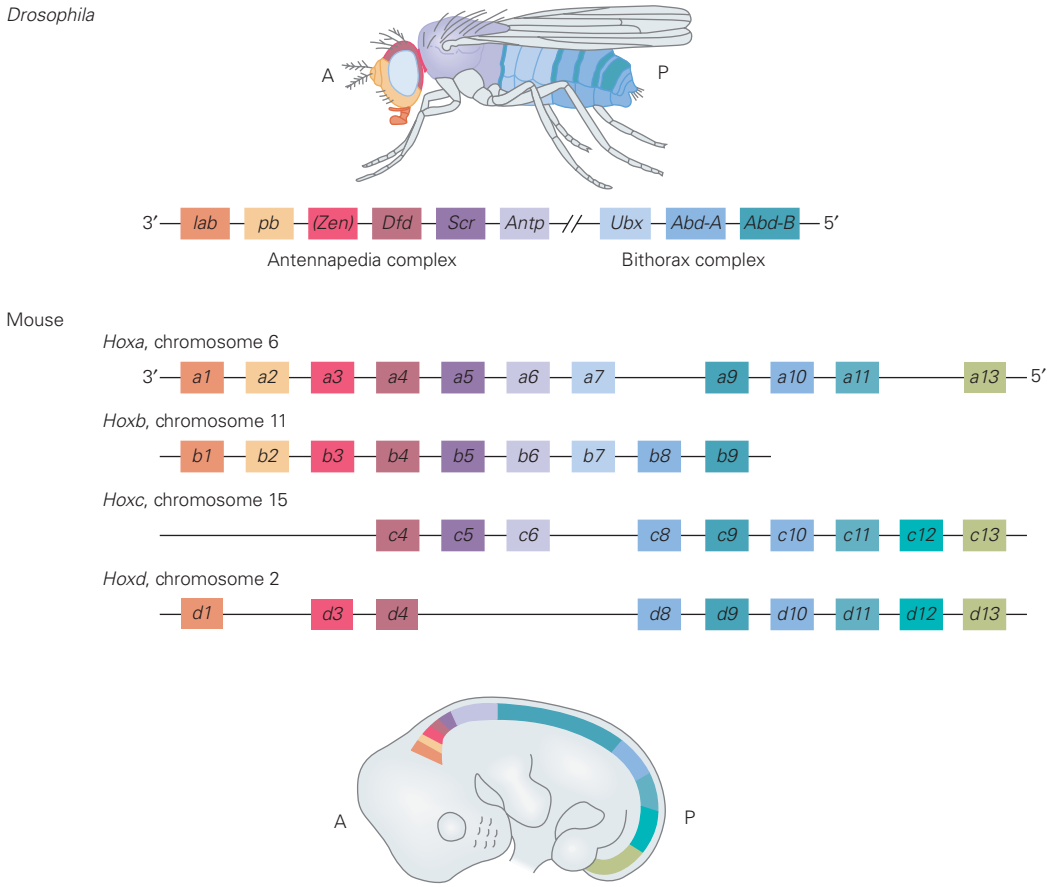

Figure 45–11 **The clustered organization of *Hox* genes is conserved from flies to vertebrates.** The diagram shows the chromosomal arrangement of *Hox* genes in the mouse and *HOM-C* genes in *Drosophila*. Insects have one ancestral *Hox* gene cluster, whereas higher vertebrates such as birds and mammals have four duplicate *Hox* gene clusters. The position of a given *Hox* or *HOM-C* gene on the chromosomal cluster is typically related to the position on the anteroposterior body axis where the gene is expressed. (Adapted, with permission, from Wolpert et al. 1998. Permission conveyed through Copyright Clearance Center, Inc.)

motor column that innervate the muscles of the forelimb (Figure 45–13A).

Repressive interactions between Hox proteins expressed by the neurons in different lateral motor columns ensure that neurons that populate different motor pools express distinct profiles of Hox protein expression. These Hox profiles direct the expression of downstream transcription factors as well as the axonal surface receptors that enable motor axons to respond to local cues within the limb that guide them to specific muscle targets. For example, the expression of Hox6 proteins activates a retinoic acid signaling pathway that directs the expression of two homeodomain transcription factors, Is11 and Lhx1. These factors in turn assign motor neurons to two divisional classes and determine the pattern of expression of the ephrin receptors that guide motor axons in the limb. The axons of motor neurons in these two divisions project into the ventral and dorsal halves of the limb mesenchyme under the control of ephrin signaling (Figure 45–14).

Not all motor neuron columns are determined by Hox protein activity, however. The median motor column is generated at all segmental levels of the spinal cord in register with axial muscles. Development of median motor column cells is controlled by Wnt4/5 signals secreted from the ventral midline of the spinal cord and by the expression of the homeodomain proteins Lhx3 and Lhx4, which render neurons in this column immune to the segmental patterning actions of Hox proteins.

Thus, in both the hindbrain and spinal cord, the point-to-point connectivity of motor neurons with specific muscles emerges through tightly orchestrated programs of homeodomain protein expression and activity. In vertebrates, these genes have evolved to

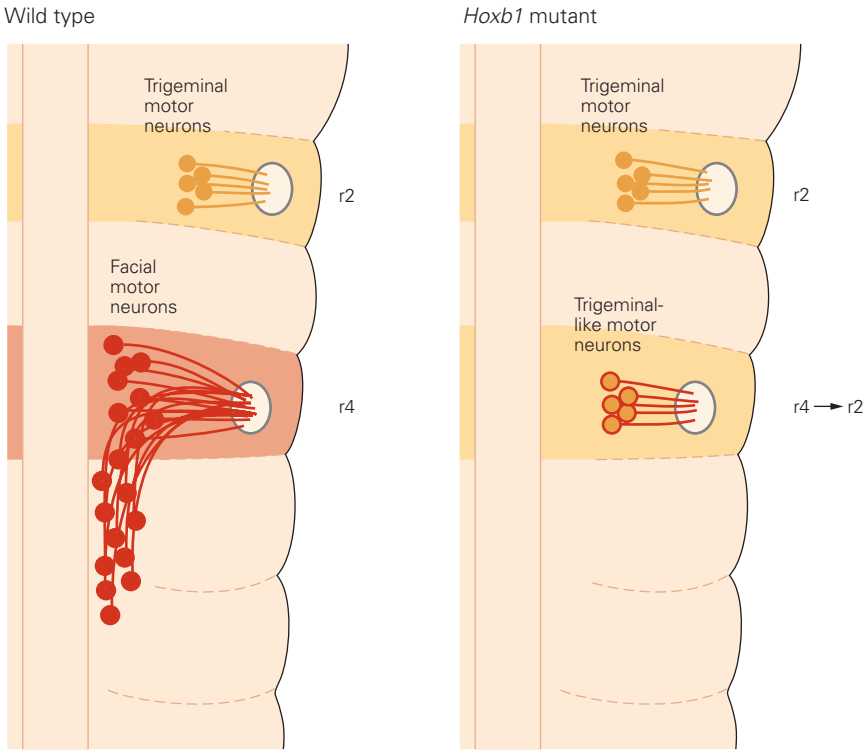

Figure 45–12 The mouse *Hoxb1* gene controls the identity and projection of hindbrain motor neurons. *Hoxb1* is normally expressed at highest levels by cells in rhombomere r4. In wild-type mice, trigeminal motor neurons are generated in rhombomere r2, and their cell bodies migrate laterally before projecting their axons out of the hindbrain at the r2 level. In contrast, the cell bodies of facial motor neurons generated in rhombomere r4 migrate caudally yet project their axons out of the hindbrain at the r4 level. In mouse *Hoxb1* mutants, motor neurons generated in rhombomere r4 migrate laterally instead of caudally, acquiring the features of r2 level trigeminal motor neurons. **Ellipses** indicate axonal exit points. (Adapted, with permission, from Struder et al. 1996. Copyright © 1996 Springer Nature.)

direct neuron subtype and connectivity as well the basic body plan.

The Developing Forebrain Is Patterned by Intrinsic and Extrinsic Influences

Neurons in the mammalian forebrain form circuits that mediate emotional behaviors, perception, and cognition and participate in the storage and retrieval of memories. Much like the hindbrain, the embryonic forebrain is initially divided along its rostrocaudal axis into transversely organized domains called *prosomeres*. Prosomeres 1 to 3 develop into the caudal part of the diencephalon, from which the thalamus emerges. Prosomeres 4 to 6 give rise to the rostral diencephalon and telencephalon. The ventral region of the rostral diencephalon gives rise to the hypothalamus and basal ganglia, whereas the telencephalon gives rise to the neocortex and hippocampus.

Inductive Signals and Transcription Factor Gradients Establish Regional Differentiation

Finally, we turn to the patterning of the neocortex itself, asking whether the developmental mechanisms and principles that govern the development of other regions of the central nervous system also control the emergence of cortical areas specialized for particular sensory, motor, and cognitive functions.

From the time of Brodmann's classical anatomical description at the beginning of the 20th century, we have known that the cerebral cortex is subdivided into many different areas. Recent studies of cortical development have begun to provide insight into the signaling mechanisms that establish somatosensory, auditory, and visual areas.

There is now evidence for the existence of a cortical "protomap," a basic plan in which different cortical areas are established early in development before inputs from other brain regions can influence development. This view is supported by studies of transcription factor expression in the developing neocortex. Two homeodomain transcription factors, Pax6 and Emx2, are expressed in complementary anteroposterior gradients in the ventricular zone of the developing neocortex—high levels of Pax6 at anterior levels and high levels of Emx2 at posterior levels. These early patterns are established in part by a local rostral source of FGF signals, which promote Pax6 and repress Emx2 expression (Figure 45–15A). As is the case in the hindbrain, the distinct spatial domains of expression of Pax6 and Emx2 are sharpened by cross-repressive interactions between the two transcription factors.

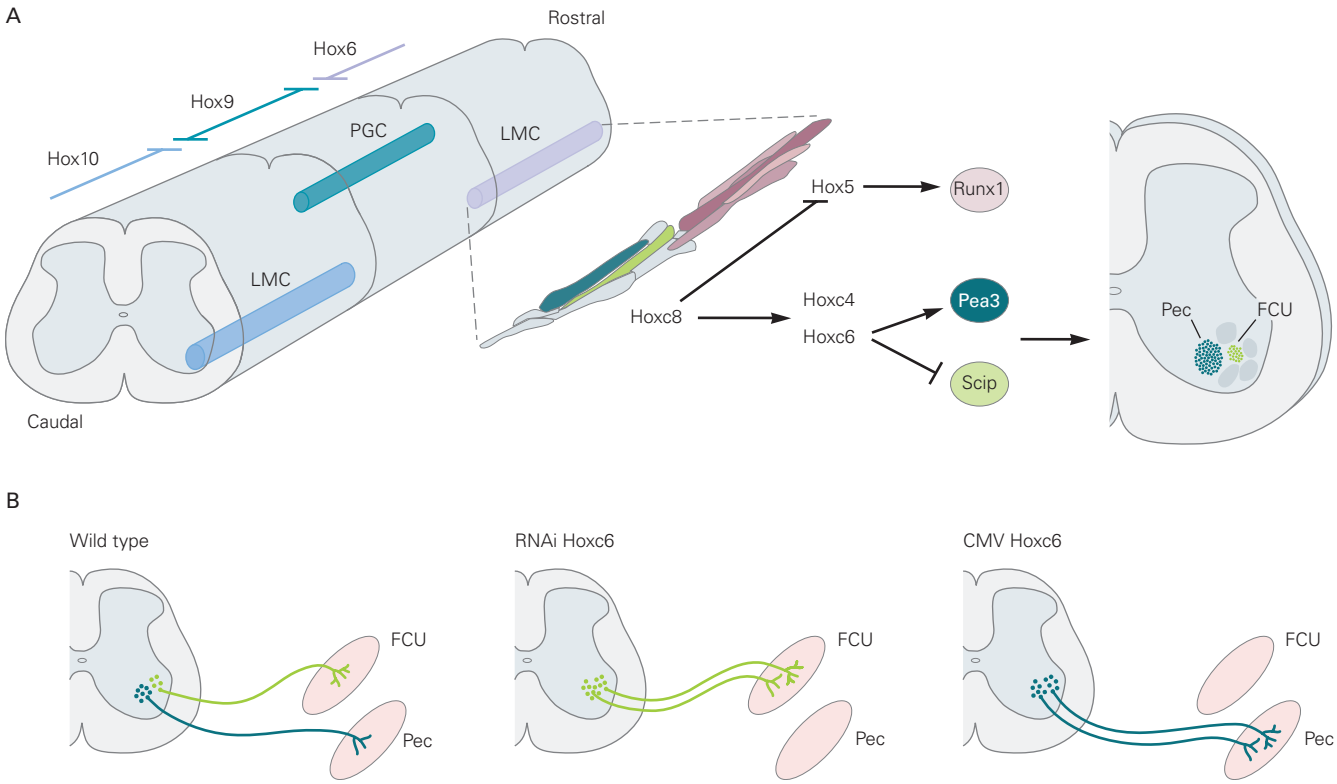

Figure 45–13 Hox proteins control the identity of neurons in motor columns and pools. (Adapted, with permission, from Dasen et al. 2005.)

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