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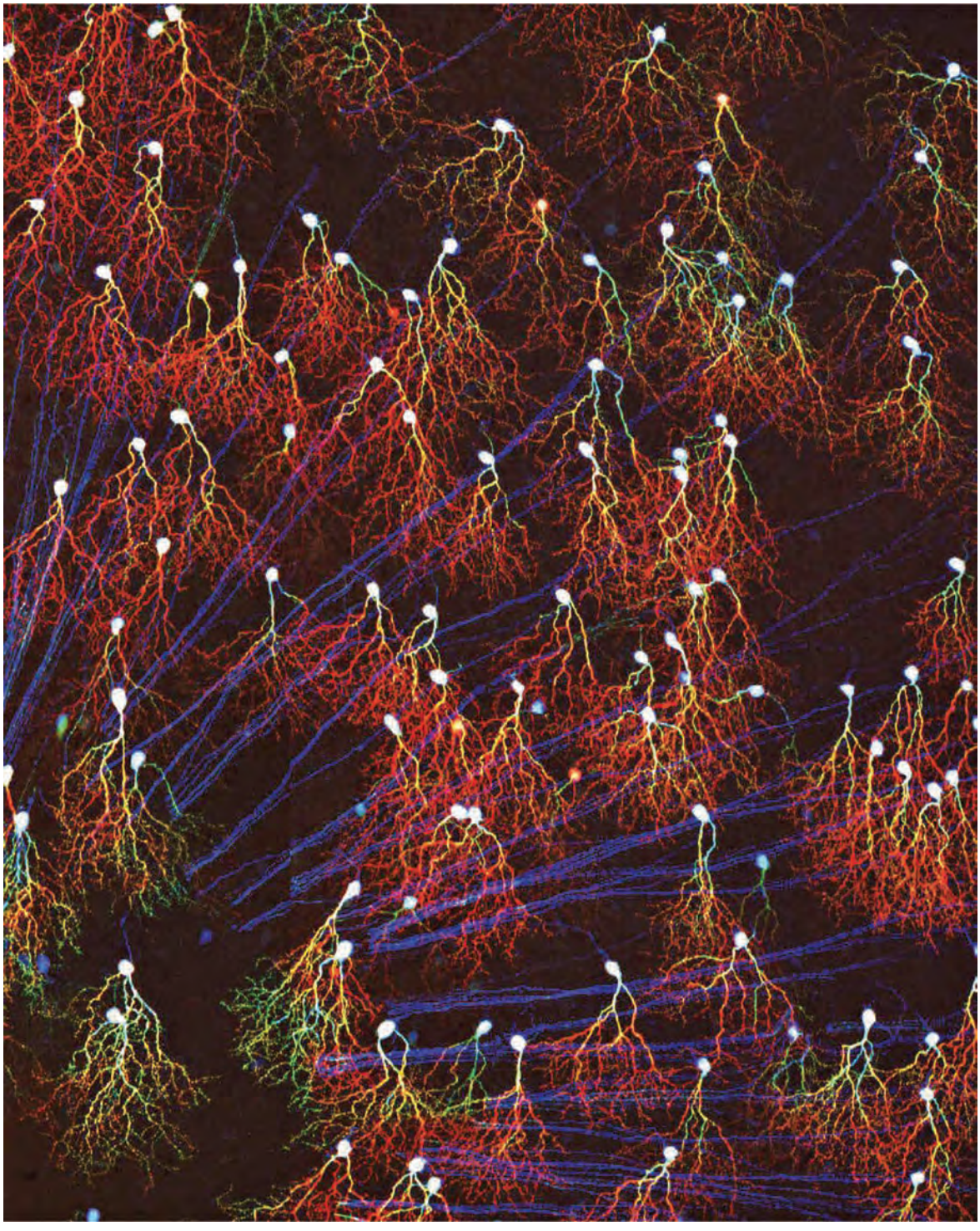
Part VII



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Transgenic labeling of a single type of retinal ganglion cell in the mouse retina. Colors represent depth through the retina, with axons at the surface in blue and the deepest dendrites in red. Incompletely understood guidance mechanisms result in J-RGC dendrites "pointing" ventrally, resulting in their preferential response to ventral motion. J-RGC axons are guided to the optic nerve through which they travel to the rest of the brain. (Reproduced, with permission, from Jinyue Liu and Joshua Sanes. Reproduced, with permission, from Journal of Neuroscience. Cover of issue 37(50), December 13, 2017; for Liu J, Sanes JR. 2017. Cellular and molecular analysis of dendritic morphogenesis in a retinal cell type that senses color contrast and ventral motion. J Neurosci 37:12247–12262.)

VII Development and the Emergence of Behavior

THE INNUMERABLE BEHAVIORS controlled by the mature nervous system—our thoughts, perceptions, decisions, emotions, and actions—depend on precise patterns of synaptic connectivity among the billions of neurons in our brain and spinal cord. These connections form during embryonic and early postnatal life but can then be remodeled throughout life. In this section, we describe how the nervous system develops and matures.

The history of developmental neurobiology is long and illustrious. Nearly 150 years ago, Santiago Ramón y Cajal undertook a comprehensive series of anatomical studies on the structure and organization of the nervous system and then set out to probe its development. The only method available to him was light microscopic analysis of fixed tissue, but from his observations, he deduced many developmental principles that are still recognized as correct. During the first half of the 20th century, other anatomists followed in his footsteps. Progress then accelerated as new methods became available—first electrophysiology and electron microscopy and, more recently, molecular biology, genetics, and live imaging. We now know a great deal about molecules that determine how nerve cells acquire their identities, how they extend axons to target cells, and how these axons choose appropriate synaptic partners once they have arrived at their destinations.

It is useful to divide the numerous steps that compose neural development into three epochs, which are conceptually distinct even though they overlap temporally to some extent. The first, beginning at the earliest stages of embryogenesis, leads to the generation and differentiation of neurons and glia. One can think of this epoch as devoted to producing the components from which neural circuits will be assembled: the hardware. These steps depend on the expression of particular genes at particular times and places. Some of the molecules that control these spatial and temporal patterns are transcription factors that act at the level of DNA to regulate gene expression. They act within the differentiating cells and are therefore called cell-autonomous factors. Other factors, called cell non-autonomous, include cell surface and secreted molecules that arise from other cells.

They act by binding to receptors on the differentiating cells and generating signals that regulate the activity of the cell-autonomous transcriptional programs. The interaction of these intrinsic and extrinsic factors is critical for the proper differentiation of each nerve cell.

A second epoch encompasses the steps by which neurons wire up: the migration of their somata to appropriate places, the guidance of axons to their targets, and the formation of synaptic connections. The complexity of the wiring problem is staggering—axons of many neuronal types must navigate, often over long distances, and then choose among a hundred or more potential synaptic partners. Nonetheless, progress has been encouraging. A major factor has been the ability to address the problem through the analysis of simple and genetically accessible organisms such as the fruit fly *Drosophila* and the nematode worm *Caenorhabditis elegans*. It turns out that many of the key molecules that control the formation of the nervous system are conserved in organisms separated by millions of years of evolution. Thus, despite the great diversity of animal forms, the developmental programs that govern body plan and neural connectivity are conserved throughout phylogeny.

In the third epoch, the genetically determined patterns of connectivity (the hardware) are molded by activity and experience (the software). Unfortunately for investigators, these steps in mammals are shared to a very limited degree with invertebrates and lower vertebrates. A newly hatched bird or fly is not remarkably different in its behavioral repertoire from its adult self, but no one could say that about a person. This is largely because our nervous system is something of a rough draft at birth. The hardwired circuits that lay out its basic plan are modified over a prolonged postnatal period by experience, acting via neural activity. In this way, the experience of each individual can leave indelible imprints on his or her nervous system and the cognitive abilities of the brain can be enhanced by learning. These processes act in all mammals, and neuroscientists now use mice to probe the mechanisms that underlie them—but they are especially prominent and prolonged in humans. It may be that the prolonged period during which experience can sculpt the human nervous system is the most important single factor in making its capabilities unique among all species.

As our understanding of development increases, it is increasingly informing neurology and psychiatry. Many genes that regulate the first two epochs have now been implicated as susceptibility factors for, or even causes of, some neurodegenerative and behavioral disorders. Thus, studies of neural development are beginning to provide insights into the etiology of neurological diseases and to suggest rational strategies for restoring neural connections and function after disease or traumatic injury. More recently, as we learn about the cellular and molecular changes that underlie experience-dependent remodeling, we can hope to understand how, for example, the plasticity that is so evident during early life can be recruited in adults to

improve rehabilitative therapy after injury, stroke, or neurodegenerative disease. Moreover, there is increasing reason to believe that some behavioral disorders, such as autism or schizophrenia, may result in part from defects in the experience-dependent tuning of neural circuits during early postnatal life.

Part VII summarizes these epochs in a sequential manner. Beginning with the early stages of neural development, we concentrate on the factors that control the diversity and survival of nerve cells, guide axons, and regulate the formation of synapses. We then explain how interactions with the environment, both social and physical, modify or consolidate the neural connections formed during early development. Finally, we examine ways in which developmental processes can be harnessed in adults and how factors such as steroid hormones mold the brain, affecting sexual and gender identity. The last steps—changes that occur as the brain ages—are covered in Section IX (Chapter 64).

Part Editor: Joshua R. Sanes

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Patterning the Nervous System

A vast array of neurons and glial cells is produced during development of the vertebrate nervous system. Different types of neurons develop in discrete anatomical positions, acquire varied morphological forms, and establish connections with specific populations of target cells. Their diversity is far greater than that of cells in any other organ of the body. The retina, for example, has dozens of types of interneurons, and the spinal cord has more than a hundred types of motor neurons. At present, the true number of neuronal types in the mammalian central nervous system remains unknown, but it is surely more than a thousand. The number of glial types is even less clear; unexpected heterogeneity is being discovered in what was thought, until recently, to be rather homogeneous classes of astrocytes and oligodendrocytes.

The diversity of neuronal types underlies the impressive computational properties of the mammalian nervous system. Yet, as we describe in this chapter and those that follow, the developmental principles that drive the differentiation of the nervous system are begged and borrowed from those used to direct the development in other tissues. In one sense, the development of the nervous system merely represents an elaborate example of the basic challenge that pervades

all of developmental biology: how to convert a single cell, the fertilized egg, into the highly differentiated cell types that characterize the mature organism. Only at later stages, as the neurons form complex circuits and experience modifies their connections, do principles of neural development diverge from those in other organs.

Early developmental principles are conserved not only among tissues but also across species and phyla. Indeed, much of what we know about the cellular and molecular bases of neural development in vertebrates comes from genetic studies of so-called simple organisms, most notably the fruit fly *Drosophila melanogaster* and the worm *Caenorhabditis elegans.* Nevertheless, because a main goal of studying neural development is to explain how the assembly of the nervous system underlies both human behavior and brain disorders, our description of the rules and principles of nervous system development focus primarily on vertebrate organisms.

The Neural Tube Arises From the Ectoderm

The vertebrate embryo arises from the fertilized egg. Cell divisions initially form a ball of cells, called the morula, which then hollows out to form the blastula. Next, infoldings and growth generate the gastrula, a structure with polarity (dorsal-ventral and anterior-posterior) and three layers of cells—the endoderm, mesoderm, and ectoderm (Figure 45–1A).

The *endoderm* is the innermost germ layer that later gives rise to the gut, as well as to the lungs, pancreas, and liver. The *mesoderm* is the middle germ layer that gives rise to muscle, connective tissues, and much of the vascular system. The *ectoderm* is the outermost layer. Most of the ectoderm gives rise to the skin, but a narrow central strip flattens out to become the *neural plate* (Figure 45–1B). It is from the neural plate that the central and peripheral nervous systems arise.

Soon after the neural plate forms, it begins to invaginate, forming the *neural groove.* The folds then deepen and eventually separate from the rest of the ectoderm to form the *neural tube*, through a process called neurulation (Figure 45–1C,D). The caudal region of the neural tube gives rise to the spinal cord, whereas the rostral region becomes the brain. As the neural tube closes, cells at its junction with the overlying ectoderm are set aside to become the neural crest, which eventually gives rise to the autonomic and sensory nervous systems, as well as several non-neural cell types (Figure 45–1E).

Secreted Signals Promote Neural Cell Fate

As with other organs, the emergence of the nervous system is the culmination of a complex molecular program that involves the tightly orchestrated expression of specific genes. For the nervous system, the first step is the formation of the neural plate from a restricted region of the ectoderm. This step reflects the outcome of an early choice that ectodermal cells have to make: whether to become neural or epidermal cells. This decision has been the subject of intense study for nearly 100 years.

Much of this work has focused on a search for signals that control the fate of ectodermal cells. We now know that two major classes of proteins work together to promote the differentiation of an ectodermal cell into a neural cell. The first are *inductive factors,* signaling molecules that are secreted by nearby cells. Some of these factors are freely diffusible and exert their actions at a distance, but others are tethered to the cell surface and act locally. The second are surface receptors that enable cells to respond to inductive factors. Activation of these receptors triggers the expression of genes encoding intracellular proteins—transcription factors, enzymes, and cytoskeletal proteins—that push ectodermal cells along the pathway to becoming neural cells.

The ability of a cell to respond to inductive signals, termed its *competence,* depends on the exact repertoire of receptors, transduction molecules, and transcription factors that it expresses. Thus, a cell's fate is determined not only by the signals to which it is exposed—a consequence of when and where it finds itself in the embryo—but also by the profile of genes it expresses as a consequence of its prior developmental history. We will see in subsequent chapters that the interaction of localized inductive signals and intrinsic cell responsiveness is evident at virtually every step throughout neural development.

Development of the Neural Plate Is Induced by Signals From the Organizer Region

The discovery that specific signals are responsible for triggering the formation of the neural plate was the first major advance in understanding the mechanisms that pattern the nervous system. In 1924, Hans Spemann and Hilde Mangold made the remarkable observation that the differentiation of the neural plate from uncommitted ectoderm depends on signals secreted by a specialized group of cells they called the *organizer region.*