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Preface

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“The brain ... is a complicated, intricately woven tissue, like nothing else we know of in the universe, but it is composed of cells, as any tissue is. They are, to be sure, highly specialized cells, but they function according to the laws that govern any other cells. Their electrical and chemical signals can be detected, recorded and interpreted and their chemicals can be identified; the connections that constitute the brain’s woven feltwork can be mapped.”

David H. Hubel

The development of the nervous system is a fantastically complex process that depends on the precise orchestration of a series of developmental events, beginning with the specification of the right kinds and numbers of neurons and glia, and culminating with their organization and refinement into inter-connected networks to form functional neural circuits. The coordinated activity of these circuits underlies our ability to perceive, move, think, feel, learn, and remember.

The process of neural development can be divided into a number of discrete, but overlapping, steps including neurogenesis, the specification of distinct types of neurons and glia, neuronal migration, axon guidance and dendrite morphogenesis, synapse formation, and activity-dependent refinement of synaptic connections. Studies using diverse experimental models and approaches have provided major insights into these developmental events; however, the mechanistic understanding of any one of these processes at the molecular level is still far from complete. Not surprisingly, disruption of these developmental events can lead to a myriad of neural developmental disorders, and knowledge gained by studying disease mechanisms can also enhance our knowledge of normal development. Indeed, important insights into the pathogenesis of neural developmental disorders originate from the study of normal development in a range of model organisms. More recently, induced pluripotent stem cells and sophisticated tissue culture techniques, complemented by the study of human mutations in animal models, have extended our understanding of these processes in humans.

12 chapters in this volume of *Current Topics in Developmental Biology* highlight the most recent advances in unraveling the molecular mechanisms of nervous system development, and how this work has enriched our understanding of developmental disorders. To cover different areas of developmental neurobiology, I recruited a diverse group of emerging or established leaders to provide snapshots of rapidly developing areas of investigation and the essential unanswered questions in their respective fields. I have given free rein to the authors to focus their chapters however they chose, and for this reason, not all of the chapters are equally weighted to the coverage of both normal development and developmental disorders.

I also encouraged investigators to include their current graduate students and postdoctoral fellows as authors on their chapters and am pleased that so many took this opportunity.

The volume opens with three chapters that focus on the development of the mammalian cerebral cortex, with a particular emphasis on neurogenesis and the diversification of cell types, and how disruptions in different aspects of normal cortical development contribute to disease. In the first chapter, Villalba, Götz, and Borrell review the current state of the art in the regulation of cortical neurogenesis. Their chapter provides a historical perspective to the field and discusses how genetic regulatory mechanisms define cell types and lineage relationships in the cortex, and how in turn deciphering these mechanisms may illuminate the understanding of the evolution of cortical neurogenesis. In the second chapter, Bond, Ming, and Song explore the origins of adult neural stem cells (NSCs) in the mammalian brain. They discuss how defining the factors and mechanisms that shape the adult NSC pool contribute to the understanding of the remarkable plasticity of the adult brain and form the foundation for the capacity for life-long neurogenesis. In the third chapter, Liu, Trupiano, Simon, Guo, and Anton provide an overview of the diverse and essential roles of primary cilia in cortical development and disorders. Their chapter reviews the intricate subcellular machinery that bestows on the primary cilium the ability to act as a critical signaling hub that integrates developmental and homeostatic signals to contribute to the normal development and function of the brain.

After the right numbers of and types of neurons and glia are specified, they must form an intricate set of connections to establish circuits. The second group of four chapters includes reviews of cellular and molecular mechanisms of axon guidance and dendrite morphogenesis, and how in turn these events allow for the precise assembly of neural circuits. In the fourth chapter, Zang, Chaudhari, and I, review current insights into how axon guidance pathways are spatially and temporally regulated and how guidance receptors signal to regulate attraction and repulsion in response to extracellular signals. In Chapter 5, Alvarez, Varadarajan, and Butler review the current understanding of the cellular and molecular mechanisms that control axon guidance of commissural neurons in the developing spinal cord. This chapter highlights the fact that even in arguably the most extensively studied axon guidance event, fundamental new discoveries are still being made. In Chapter 6, Lefebvre turns our attention to the mechanisms that mediate dendrite morphogenesis, drawing examples from work in multiple experimental systems that highlight key concepts in how proper shaping and elaboration of dendritic territories underlies information flow in neural circuits. In Chapter 7, Johnson and Triplett highlight the mechanisms of axon guidance and targeting in the context of building and aligning sensory maps in the visual system. Their review describes both activity-independent and -dependent mechanisms that allow the retina, superior colliculus, and cortex to construct aligned representations of visual space.

Once axons and dendrites form, navigate to the correct regions, and acquire their complex arborization patterns, they must form synapses with the correct partner neurons. The precise recognition and choice of synaptic partners are made even more challenging to understand, because of the fact that the “correct” partners are intermingled with a large number of incorrect targets in neurite dense neuropil structures. The next two chapters in the volume

focus on the mechanisms of synapse formation and maturation, with an emphasis on the critical roles of diverse families of conserved synaptic adhesion molecules and the essential functions that are mediated by astrocyte–neuronal interactions to regulate these events. In Chapter 8, Chowdhury, Watters, and Biederer catalog the large repertoire of trans-synaptic adhesion molecules, and highlight the mechanisms that allow these molecules to control initial wiring decisions, to reject incorrect partner choices, to promote maturation, and to contribute to synaptic pruning. In Chapter 9, Tan, Lane, and Eroglu describe the growing body of literature that has identified key roles for astrocytes in providing instructive signals to promote synapse formation and maturation. This chapter illustrates the importance of bidirectional adhesion and secretion-based interactions between neurons and glia that underpin normal synapse formation and function. Both chapters also discuss the implications of perturbing these developmental mechanisms for neural disease.

In order to think more holistically about how discrete steps of neuronal circuit development instruct specific behavioral outputs at the organismal level, it is useful to focus on the development of distinct neuronal systems that are dedicated to specific functions. The next two chapters review recent work that is directed at understanding the development of motor circuits and somatosensory circuits, respectively. In Chapter 10, Meng and Heckscher discuss how stem cells generate specific cohorts of neurons that function together in mature motor circuits, with a particular focus on the *Drosophila* larval motor system. This chapter highlights how precisely timed expression of temporal transcription factors contributes to motor circuit assembly by regulating the fate, maturation and synaptic partner choice of discrete groups of neurons. In Chapter 11, Cranfill and Luo review the mechanisms underlying the development of somatosensory circuits, with a particular emphasis on how extrinsic and intrinsic programs are integrated to control the diversification of somatosensory neurons. In addition, this chapter illustrates how understanding the organization of somatosensory circuitry can offer insights into normal processing of pain and itch sensation, as well as disease processes underlying congenital pain-related disorders.

While studies using a diverse array of animal models have provided and will continue to provide important conceptual advances that have fueled the understanding of normal development and neural developmental disorders, these models are inherently limited because they do not adequately recapitulate human-specific features that are relevant to disease. Hence, there is a clear need to develop tools and methods to more directly study neural development and the pathogenesis of disease in humans. In 12th and final chapter of this volume, Jacob, Schnoll, Song, and Ming, describe the exciting development of new technologies to generate region-specific human brain organoids to study development and disease. As some of the pioneers of these techniques, Song, Ming, and their colleagues describe recent advances that are allowing investigators to better mimic the *in vivo* developing human brain, as well as describing obstacles that need to be overcome to maximize the potential of these technologies for future studies.

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