Preface

The functions of nervous systems range from simple behaviors to conscious thought, and for well over a century scientists have striven to decipher the wiring diagram of complex neural circuits and to identify the mechanisms that are responsible for establishing these precise neuronal connections during embryonic development. The intricate and seemingly infinite potential for unique contacts among the massive number of neuronal processes in the mammalian brain underscores the challenge of defining how this connectivity is achieved. Even the somewhat simpler nervous systems of model organisms such as flies and worms, though orders of magnitude less intricate, are wonderfully complicated assemblages of myriad interconnected circuits, and our understanding of precisely how these circuits are established is still in its infancy. Nevertheless, it has long been appreciated that nervous system wiring is intimately related to function, and therefore a central goal in neuroscience research has been to define the cellular, and more recently molecular, mechanisms that orchestrate the establishment of neuronal connectivity. Fortunately, work over the past several decades has greatly advanced our understanding of these mechanisms.

Our goal in compiling this volume is to provide a reasonably comprehensive perspective on what is known about the major neuronal guidance events that collectively define the various facets of neuronal connectivity. We have attempted to showcase work from many different experimental systems that together provide a broad overview of our current understanding and a foundation for future work that will continue to elucidate the origins of intricate neuronal connections.

The first section of this book considers our current understanding of axon and dendrite guidance and branching strategies. Chapters in this section focus on the basic cellular strategies and molecular mechanisms that serve to establish axonal and dendritic trajectories, including an enumeration of major known guidance cues and their receptors. The operation of these cues is discussed in the context of important guidance phenomena such as the navigation of intermediate targets and arrival at final targets, laminar organization, and the spacing of dendritic processes. Sensory neuron projections to their CNS targets provide intriguing examples of complex neuronal guidance events that are intimately linked to the processing of distinct sensory modalities, and so we have included consideration of topographic mapping strategies employed in the visual and olfactory systems. Key events in the assembly of the mammalian brain are also discussed, as well as emerging work in human genetics that shows how deficits in these mechanisms result in characteristic syndromes that shed light on functional nervous system organization.

The second section is devoted to the intracellular signaling events that are required for the guidance of neuronal processes, and which are triggered both as part of cell-autonomous morphogenetic programs and in response to extracellular cues. How neurons initially elaborate distinct axonal and dendritic processes is a key issue and is considered in the context of the extracellular and intracellular events that govern this process. Intracellular signaling events that direct the organization of axonal and dendritic cytoskeletal components are being defined and are discussed in this section, along with how guidance cue receptors directly act upon these signaling cascades to attract or repel neuronal processes. Additional cellular events play key roles in regulating how neuronal processes are guided; one of those considered here is how guidance cue receptors are trafficked to different cellular compartments or portions of the axon.

The third and final section of this book summarizes the mounting evidence that axon guidance molecules are used for a variety of other cellular processes. Within the nervous system, these include neuronal cell body migration, the pruning back of established axonal and dendritic projections, and the regulation of neuronal cell death. Of great interest is the role played by developmental guidance cues and mechanisms at later times in adult life, including their influence on neuronal regeneration following injury or degeneration. It is also becoming increasingly apparent that axon guidance cues and mechanisms play key roles in the regulation of synaptogenesis and synaptic plasticity, and this issue is explored in both invertebrate and vertebrate systems. Finally, guidance cues first identified in the context of the nervous system are now appreciated to function in most every other organ system, and this volume concludes with a consideration of guidance cue signaling in vascular development and patterning.

What emerges from these chapters is a rich understanding of numerous aspects of neuronal circuit morphogenesis. But they also highlight the many gaps in our knowledge. In no case has it been possible to enumerate all of the cues required to guide a given axon from its cell body of origin to its final targets. While progress has been made in identifying signal transduction components, again in no case has the full pathway from activation of a guidance receptor to cytoskeletal rearrangements and altered cellular steering been described. How growth cones switch their responses to guidance cues from attraction to repulsion at intermediate targets remains largely mysterious, and whether this plasticity of growth cone responses is reused for other aspects of nervous system plasticity or for responses to injury also remains unknown. While some initial insights into topographic map formation have been obtained, how axons can show the exquisitely graded responses required to establish smooth maps still remains poorly understood. And whether deficits in guidance mechanisms will contribute not just to neurological but also to psychiatric disorders is not yet known. These and other issues represent key challenges for coming years. It is our hope that the present volume will serve as a useful reference point as investigators plan their attack on these outstanding questions.

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