

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.

We wish to thank Richard Sever, Cold Spring Harbor Laboratory Press, for bringing this project to life, and Kaaren Kockenmeister for her excellent work on the production of this volume. We also thank Joan Ebert for her perseverance in managing the manuscripts in this book and facilitating completion of this project. For the cover photograph, we are indebted to Nyoman Kurniawan, Randal Moldrich, and Linda Richards of The University of Queensland, Queensland Brain Institute and the Centre for Advanced Imaging. Last but not least, we are extremely grateful to all of the authors for participating in this project. Their contributions to this volume are insightful and provide a definitive snapshot of the state-of-the-art today. Their chapters provide a valuable context for the next decades of work devoted to understanding how complex brain wiring is achieved during neural development.

MARC TESSIER-LAVIGNE

ALEX L. KOLODKIN

Index

A

- α 2-chimaerin, 265
- Ableson (Abl), 214–216
- Actin/MT cross-linking proteins, 221
- Actin-nucleating proteins, 220–221
- Adenomatous polyposis coli (APC), 182–183, 225
- AIS (axon initial segment), 280–282
- AIY and synaptogenesis, 315
- AKT, 182, 186. *See also* Axon growth and initiation
- Albinism, 169–170
- AnkyrinG, 151
- Anosmia, 168
- APC (adenomatous polyposis coli), 182–183, 225
- apCAM, 204
- ApoER2, 299–301
- Arbors, axonal. *See* Dendrite and axon spacing mechanisms
- ARP2/3 complex, 220
- Axo-dendritic synaptogenesis. *See* Synaptogenesis
- Axon growth and initiation
 - conclusions and future studies, 192
 - cytoskeletal dynamics and axon initiation, 182
 - extracellular cues regulating axon growth
 - elongation control, 190–192
 - neuronal activity requirement, 190
 - extracellular cues regulating neuronal polarization
 - Laminin, BDNF and Sema3A, 190
 - Netrin-1 and Wnt, 189–190
 - in vitro, 179–180
 - in vivo, 181
 - local protein degradation and axon specification, 181–182
 - local protein translation and neuronal polarization, 182
 - microtubule dynamics and axon elongation, 182–183
 - Rho and Ras GTPases and
 - axon growth, 243–245
 - GSK-3 phosphorylation and inhibition, 242
 - loss-of-function studies, 243
 - neuronal polarization model, 240–242
 - Rac-mediated phosphorylation, 242–243
 - signaling pathways involved
 - AKT/Protein Kinase B, 186
 - GSK-3, 186–187
 - JNK signaling, 188
 - LKB1, SAD-A/B, and MARKs, 183–184
 - PAR3-PAR6-aPKC, 184–185
 - PI3K-kinase signaling, 185–186
 - PTEN, 186
 - RAF/MEK/ERK regulation, 187–188
 - Ras- and Rho-family of small GTPases, 185
 - transcription regulators, 188–189
 - specification regulation versus growth cues, 181
- Axon initial segment (AIS), 280–282
- Axon pruning and cell death
 - conclusions and future studies, 341–342
 - guidance molecules
 - apoptosis effectors and regulators, 341
 - ephrins and eph, 335–336, 340–341
 - intrinsic and extrinsic factors, 333–334
 - netrins and their receptors, 339–340
 - neuropilin, 334–335
 - other related molecules, 336, 341
 - plexin, 334–335
 - semaphorin, 334–335, 340
 - large-scale stereotyped pruning
 - in the cerebral cortex, 331, 332f
 - in the hippocampus, 331–333
 - in topographic maps, 333
 - neural cell death and development
 - early death and brain morphogenesis, 338–339
 - neurotrophic model, 338
 - overview, 336–338
 - regressive events in diseases, 330
 - regressive events in neuronal development, 329–330
 - small-scale pruning model, 330–331
- Axon regeneration
 - conclusions and future studies, 361
 - ephrins and eph, 353
 - extracellular matrix molecules and axonal growth
 - after injury, 357–359
 - growth factors role in the injured CNS, 359–361
 - guidance molecules post-injury role, 350, 352
 - limits to regenerative growth in CNS and PNS, 349, 351t
 - mechanisms of myelin-associated growth inhibition, 355–356
 - prototypic myelin inhibitors, 354–355
 - regenerative capacity of injured CNS, 348–349
 - regulation of neuronal plasticity, 356–357
 - regulation of neuronal structure and, 349–350
 - semaphorins, 352–353
 - Wnt proteins, 353

- Axons
- adhesive cues, 24–25
 - axon–axon interactions in vivo, 20, 22
 - distribution and regulation of guidance receptors and cues, 27–28
 - extension in vivo, 15–16, 17f
 - glial cells and axon outgrowth, 20, 21f
 - growth cones' use of neuronal cells, 22–24
 - guidance of commissural, 38–41
 - initiating and growing (*see* Axon growth and initiation)
 - integration of guidance information, 28–29
 - interstitial spaces' role in axon growth, 18, 20
 - limits of categorization, 26–27
 - midline cells guidance, 37–38, 39f
 - modulatory guidance cues, 26
 - pioneer neurons, 16, 18, 19f
 - preference for growth on immature glial, 22, 23f
 - pruning and cell death (*see* Axon pruning and cell death)
 - regeneration (*see* Axon regeneration)
 - spacing mechanisms (*see* Dendrite and axon spacing mechanisms)
 - trophic signals from neurotrophins, 25–26
 - tropic guidance cues, 26
- B**
- bantam*, 101
- Barbed-end binding proteins, 205
- Basement membrane, 83–84
- BDNF/TrkB, 316–317, 321–322
- BMP7, 203, 218
- BMP receptors, 7
- Boundary cap (BC) cells, 57–59
- Brain-derived neurotrophic factor (BDNF), 183, 190, 316–317, 359
- Bristles
- growth cone cytoskeleton and, 219
 - monomer binding proteins
 - actin/MT cross-linking proteins, 221
 - actin-nucleating proteins, 220–221
 - CAP, 220
 - profilin, 219–220
- C**
- Cadherins, 24–25, 58, 65, 82–83, 97
- Caenorhabditis elegans*
- axon initiation in vivo, 181
 - axon pruning and cell death and, 336
 - midline cells and, 40
 - morphogens and growth factors in, 7
 - motor axon guidance analysis in, 264
 - netrins in, 2–4
 - Slit and, 4
 - synaptogenesis and, 315
 - tiling mechanism in, 100
- Calcium, 261–262
- Calcium-induced calcium release (CICR), 261
- CAMs. *See* Cell adhesion molecules
- CAP (cyclase associated protein), 219, 220
- Capase 3/6, 341
- Capping protein (CP), 210–211
- CC (corpus callosum) dysgenesis, 164
- CC2, 207
- CCDDs (congenital cranial dysinnervation disorders), 162, 170–171
- CDK5, 295, 297–298, 299
- Cell adhesion molecules (CAMs)
- adhesive cues and, 24–25
 - control of neuron targeting and, 151
 - guidance role described, 8–9
 - L1/NgCAM (*see* L1/NgCAM)
 - lamina-specific axon targeting and, 81–82
 - self-avoidance mechanisms role, 91–92, 93f
- Central nervous system (CNS), 291. *See also* Axon regeneration
- Cerebellar granule neuron (CGN), 181
- Cerebral cortex, 292–293, 331, 332f
- CFEOM1 (congenital fibrosis of the extraocular muscles type 1), 170–171
- CHL1 (L1), 151
- Chondroitinase ABC (ChABC), 357–359
- Chondroitin sulfate proteoglycans (CSPGs), 250, 349, 357–359
- CICR (calcium-induced calcium release), 261
- c-Jun amino-terminal kinase (JNK), 188
- CLASP, 222, 225
- CLIP (Cytoplasmic Linker Protein), 222
- CNG (cyclic nucleotide gated) channel, 128
- CNS (central nervous system), 291. *See also* Axon regeneration
- Cofilin, 203, 217–218
- Collapsin-1, 4
- commisureless (comm)*, 41–44
- Congenital cranial dysinnervation disorders (CCDDs), 162, 170–171
- Congenital fibrosis of the extraocular muscles type 1 (CREOM1), 170–171
- Connexins, 299
- Corpus callosum (CC) dysgenesis, 164
- CP (capping proteins), 210–211
- CPG15, 341
- CRD-Nrg1 (type III Nrg1), 302
- CRMP family, 226
- CSPGs (chondroitin sulfate proteoglycans), 250, 349, 357–359
- Cxcl12 ligand, 57
- Cxcr4:Cxcl12 signaling, 57, 58–59
- Cxcr4 receptor, 57
- Cyclase associated protein (CAP), 219, 220

Cyclic nucleotide gated (CNG) channel, 128
Cyclic nucleotides, 262–263
Cytoplasmic Linker Protein (CLIP), 222

D

da (dendritic arborization) neurons, 91, 96, 100
DAAMI (disheveled-associated activator of morphogenesis), 209–210
Dab1 (Disabled-1), 299, 300–301
DCC (deleted in colorectal cancer)
 actin-associated proteins in axon guidance, 208
 axon guidance and, 250
 axon guidance receptors signaling and, 259
 commissural axons guidance and, 39
 integration of guidance information and, 29
 link to activation of guidance receptors, 264
 neural cell death and, 339–340
 proteolytic processing and receptor signaling, 260
 tropic guidance cues and, 26
DCLK (Doublecortin-like kinase), 297
DCX (Doublecortin), 295–298
Death receptor 6, 336
Delta-like 4 (Dll4), 374
Dendrite and axon spacing mechanisms
 conclusions and future studies, 101
 heteroneuronal tiling mechanisms
 common features of tiling process, 94, 95f
 homotypic interactions in *Drosophila*, 97
 neighbor interactions and intrinsic limits in the retina, 94–96
 neighbor interactions limiting somatosensory axon territories, 96–97
 tiling behavior of peripheral sensory neurons, 96
 isoneuronal spacing mechanisms, 90–91
 maintenance of tiling, 100–101
 map formation in *Drosophila*, 136–138
 molecular mechanisms of tiling
 in *Drosophila* da neurons, 100
 Dscam2 mediation in *Drosophila*, 99–100
 regulation of axon spacing in the fly visual system, 97, 98f, 99
 self-avoidance mechanisms
 cell surface receptors involved, 93–94
 possible cell adhesion molecules role, 91–92, 93f
 self-recognition mechanism study, 91
 tiling defined, 89–90
Dendritic arborization (da) neurons, 91, 96, 100
Derailed (Drl), 7, 47
Diffusion spectrum imaging (DSI), 163
Diffusion tensor imaging (DTI), 163
Disabled-1 (Dab1), 299, 300–301
Disheveled-associated activator of morphogenesis (DAAM1), 209–210
dLGN (dorsal lateral geniculate nucleus), 106

Dll4 (Delta-like 4), 374
dMP2, 49f
DOCK7, 242
Dorsal lateral geniculate nucleus (dLGN), 106
Dorsal root ganglia (DRG), 96, 340
Doublecortin (DCX), 295–298
Doublecortin-like kinase (DCLK), 297
Down syndrome cell adhesion molecule 1 (Dscam1).
 See Dscam family/Dscam1
Dpod1, 221
DRAL, 341
DRG (dorsal root ganglia), 96, 340
Drosophila
 Abl and, 215
 actin-associated proteins in axon guidance, 207, 210, 211
 actin/MT cross-linking proteins and, 221
 axon branching and, 251–252
 axon growth in vivo studies, 245
 CAMs in, 9
 dendrite and axon spacing mechanisms, 97, 99–100
 guidance molecules in axon pruning, 333–334
 mechanisms of axon guidance in the brain and, 285
 midline cells (*see* Midline cells)
 morphogens and growth factors in, 7
 motor axon guidance analysis is, 264–265, 267
 netrins in, 2–4
 olfactory system, 135–138
 proteolytic processing and receptor signaling, 259–260
 Semaphorins and, 6
 signaling from axon guidance receptors and, 262–263
 Slit and, 4
 visual system organization, 75–76, 82–83
DRS (Duane retraction syndrome), 171–172
Dscam family/Dscam1
 commissural axons guidance and, 39
 guidance role described, 9
 lamina-specific axon targeting and, 81
 mediation of tiling, 99–100
 self-avoidance mechanisms and, 92, 93f, 99
 tropic guidance cues and, 26
DscamL, 81
DSI (diffusion spectrum imaging), 163
DTI (diffusion tensor imaging), 163
Duane retraction syndrome (DRS), 171–172
Dynein, 227, 297

E

Ecdysone receptor, 333
ECM (extracellular matrix), 24, 84–85
ECs (endothelial cells), 369. *See also* Vascular patterning

- ELF-1 (Eph Ligand Family-1), 107
Enabled (Ena), 207
 Ena/VASP proteins, 205, 207–209
 Endocytosis, 257–259
 Endosomal systems, 275–276
 Endothelial cells (ECs), 369. *See also* Vascular patterning
En passant synapses, 314
 Eph Ligand Family-1 (ELF-1), 107
 Ephrin-A:EphA system
 axon guidance and, 248–250
 axon guidance receptors signaling and, 257–259
 axon pruning and cell death and, 335–336
 axon regeneration and, 353
 control of neuron targeting and, 151–152
 forward signaling and activation of guidance receptors, 265–266
 guidance role described, 6–7
 motor axon guidance and, 62–64
 neural cell death and, 340–341
 neuronal migration and, 304
 proteolytic processing and receptor signaling, 259–260
 reverse signaling and activation of guidance receptors, 266–267
 synaptogenesis and, 318, 319, 322–323
 vascular patterning by axon guidance molecules and, 379–381
 visual map development and, 107
 EPS8, 211
 ErbB4, 302
 Extracellular matrix (ECM), 24, 84–85
 Ezrin, radixin, moesin (ERM), 211
- F**
- F-actin (filamentous actin), 200f. *See also* Growth cone cytoskeleton
 FAK (focal adhesion protein), 298
 Fasciclin II (FasII), 48
 Fasciclin IV, 4
 Fascin, 213–214
 Fgfs
 mechanisms of axon guidance in the brain and, 148
 neuronal guidance and, 144, 145, 146
 as selective chemoattractants for MMC cells, 60–62
 Fibrillar actin (F-actin), 10
 Filamin A, 299
 Filopodia, 200–201
 Fish
 organization of the visual system (*see* Lamina-specific axon targeting)
 topographic map development, 107–109
 Flamingo (Fmi), 97, 99, 100
 Fly. *See* Insects
 Fmi (Flamingo), 97, 99, 100
 Focal adhesion protein (FAK), 298
 Frizzled 3, 7
 Frizzled-related proteins (sFRPs), 47
 Frogs, 107–109
 Furry (fry), 100
- G**
- GABAergic interneurons, 292. *See also* Neuronal cell migration guidance
 G-actin, 202
 Ganglion-cell layer (GCL), 75
 GAP-43, 216
 Gap junctions, 299
 GAPs (GTPase-activating proteins), 239.
 See also Rho and Ras GTPases
 GCL (ganglion-cell layer), 75
 GEFs (guanine nucleotide exchange factors), 239
 Gelsolin, 211, 217
 Glial cell line-derived neurotrophic factor (GDNF), 64
 Glial sling, 303–304
 Golden goal (GOGO), 99
 Golgi outposts, 275
 Gonadotropin-releasing hormone (GnRH), 168
 G protein-coupled receptors (GPCRs), 126.
 See also Olfactory system
 Growth and initiation of axons. *See* Axon growth and initiation
 Growth cone cytoskeleton
 actin-associated proteins in axon guidance
 accessory proteins, 205, 206f
 barbed-end binding proteins, 205
 capping proteins, 210–211
 DAAM1, 209–210
 Ena/VASP proteins, 205, 207–209
 MRL proteins, 209
 actin depolymerizing proteins, 218–219
 actin dynamics in growth cone protrusion, 201–203
 axon outgrowth stages, 201
 F-actin binding proteins
 Abl, 214–216
 ERM, 211–212
 fascin, 213–214
 GAP-43, 216
 Myosin-II, 216–217
 Spectrin, 216
 UNC-44, 216
 UNC-115/ablim, 212–213
 F-actin severing proteins, 203, 217–218
 form and function of the axonal growth cone, 200–201
 microtubule dynamics in axon guidance, 10, 203–205

model for cytoskeletal function, 227–229
monomer binding proteins, 219–221
MT-associated proteins in axon guidance, 223–224t
 MT-destabilization and severing, 226–227
 MT motor proteins, 227
 MT-stabilizing proteins, 225–226
 +TIP proteins, 222, 225
GSK-3, 186–187
GTPase-activating proteins (GAPs), 239.
 See also Rho and Ras GTPases
Guanine nucleotide exchange factors (GEFs), 239
Guidepost cells, 303–304

H

HARDI (high angular resolution diffusion imaging),
 153
Hebbian models, 119
Hepatocyte growth factor (HGF), 25
HGPPS (horizontal gaze palsy with progressive
 scoliosis), 167–168
HH (hypogonadotropic hypogonadism), 168
High angular resolution diffusion imaging
 (HARDI), 153
Hippocampus, 331–333
HMC (hypaxial motor column), 54f
Horizontal gaze palsy with progressive scoliosis
 (HGPPS), 167–168
HOX-class of transcription factors, 55–57
Human genetic disorders of axon guidance
 conclusions and future studies, 172
 of cranial nerve guidance
 albinism, 169–170
 CFOEM1, 170–171
 Duane retraction syndrome, 171–172
 Kallmann syndrome, 168–169
 pontine tegmental cap dysplasia, 172
 detection of disorders, 162–163
 of midline crossing
 corpus callosum dysgenesis, 164
 horizontal gaze palsy, 167–168
 Joubert Syndrome, 166–167
 L1 syndrome, 164, 166
 summary, 163–164, 165t
 synkinesis, 161–162
Hypaxial motor column (HMC), 54f
Hypogonadotropic hypogonadism (HH), 168

I

IgCAM (immunoglobulin superfamily), 24–25, 151
IGF (insulin-like growth factor), 25
Ig-Nrg1 (type I/II Nrg1), 302
Inner nuclear layer (INL), 75
Insects (fly)
 olfactory system

axon guidance and dendritic patterning,
 136–138
development specification of input and output
 neurons, 135–136
divergent olfactory signaling mechanisms,
 126, 128–129
glomerular targeting mechanisms, 135
odorant receptor gene choice, 129–130
sensory neurons and odorant receptor
 proteins, 127f
spatial organization of antenna, 130
topographic mapping in antennal lobe, 131
visual system, 75–76, 82–83
Insulin-like growth factor (IGF), 25
Integrins, 298–299
Invertebrate midline cells. *See* Midline cells

J

JNK (c-Jun amino-terminal kinase), 188
Joubert Syndrome and related disorders (JSRD),
 166–167

K

Kalirin-7, 318
Kallmann syndrome (KS), 168–169
Katanin, 226–227
KIF5, 281, 282
Krox20, 58
Kuzbanian/ADAM10 family, 259

L

L1, 259
L1 (CHL1), 151
L1-CAM, 151
L1/NgCAM
 axonal enrichment of receptors role, 274, 276
 control of guidance receptor distribution at
 growth cones and, 282–284
 transcytosis and, 277–278
L1 syndrome, 164, 166
Lamellipodia, 200
Lamina-specific axon targeting
 by cell–cell recognition
 categories of models, 79, 80f
 lamination in the *Drosophila* visual system,
 82–83
 specific cell-surface adhesion molecules,
 79, 81–82
 chemoaffinity principle in topographic mapping,
 73–74
 conclusions and future studies, 86
 guidance by matrix cues and secreted
 factors, 83

- Lamina-specific axon targeting (*continued*)
- in vivo observations of layer formation of zebrafish IPL, 77–79
 - influence of neural activity on lamina-specific connections, 85–86
 - patterning by basement membrane-anchored cues, 83–84
 - patterning by extracellular matrix factors, 84–85
 - synapses concentration, 74
 - visual system organization
 - photoreceptor axon targeting in *Drosophila*, 75–76
 - synaptic specificity steps, 75
 - vertebrate retina, 75
 - vertebrate retinotectal projection, 76–77
- Laminin
- adhesive cues and, 24
 - extracellular cues regulating neuronal polarization, 190
 - tropic guidance cues and, 26
- Lateral ganglionic eminence (LGE), 302
- Lateral motor column (LMC), 54f
- Lateral olfactory tract (LOT), 147, 304
- Leading process dynamics, 293–295.
- See also* Neuronal cell migration guidance
- Leukocyte Antigen Related (LAR) protein, 93
- LGE (lateral ganglionic eminence), 302
- LIM-HD class of transcription factors, 55–56
- LIN-44/Wnt, 314–315
- Lissencephaly 1 (Lis1), 295–298
- LKB1, 183–184
- LMC (lateral motor column), 54f
- Long-term depression (LTD), 321–322
- Long-term synaptic potentiation (LTP), 321–322
- LOT (lateral olfactory tract), 147, 304
- Lysophosphatidic acid (LPA), 341
- M**
- MAG (myelin-associated glycoprotein), 250, 349, 354–356
- Mammals (mice)
- development of dopaminergic projections, 148, 149f
 - olfactory system
 - axonal convergence and topographic mapping, 130–131
 - divergent olfactory signaling mechanisms, 126, 128–129
 - odorant receptor gene choice, 129–130
 - sensory neurons and odorant receptor proteins, 127f
 - spatial organization of olfactory epithelium, 130
 - olfactory system map formation
 - activity-dependent refinement, 135
 - axon–axon interactions, 132–133
 - epithelium and bulb correlations, 131–132
 - neuronal activity-dependent local axon sorting, 133–135
 - OR-instructed glomerular positioning, 132
 - organization of the visual system (*see* Lamina-specific axon targeting)
- MAPIB, 221, 226
- Marcus Gunn phenomenon, 162f
- MARKs, 183–184
- MASA syndrome, 274
- Medial ganglionic eminence (MGE), 302
- Medial longitudinal fasciculus (MLF), 144
- Medial motor column (MMC), 54f
- Mesencephalic nucleus (MesV), 144
- Mical, 218–219
- Microtubule (MT), 10. *See also* Growth cone cytoskeleton
- associated proteins table, 223–224t
 - destabilization and severing, 226–227
 - dynamics in axon guidance, 200f, 203–205
 - motor proteins, 227
 - stabilizing proteins, 225–226
 - +TIP proteins, 222, 225
- Midline cells
- anterior-posterior guidance decisions, 45–46
 - axon guidance and, 37–38, 39f
 - commissural axons guidance, 38–41
 - conclusions and future studies, 48–50
 - general principles, 49–50
 - human genetic disorders of midline crossing
 - corpus callosum dysgenesis, 164
 - horizontal gaze palsy, 167–168
 - Joubert Syndrome, 166–167
 - L1 syndrome, 164, 166
 - ipsilateral or contralateral pathway choice, 41–44
 - longitudinal pathways formation, 47–48, 49f
 - switching of response after crossing the floor plate, 44–45
- Migration of neuronal cells. *See* Neuronal cell migration guidance
- MLCK (Myosin Light Chain Kinase), 217
- MLF (medial longitudinal fasciculus), 144
- MMC (medial motor column), 54f
- Monoamine oxidase B*, 58
- Motor neurons
- boundary cap cells, 57–59
 - conclusions and future studies, 65–66
 - diversity development
 - HOX-class of transcription factors, 56–57
 - identity assignment, 55
 - LIM-HD transcription factors, 56
 - motor pool identity control, 56–57
 - subtype diversification, 53, 54f, 55
 - transcription families involved, 55–56
 - LMC guidance within the limb, 62–64

- MMC projections to axial muscles, 60–62
- motor axon growth from the neural tube, 57
- motor pool branching on individual muscles, 64–65
- spinal nerves and segmental patterning, 59–60
- transaxonal signaling contribution, 65–66
- Mouse. *See* Mammals (mice)
- MRL proteins, 209
- MT. *See* Microtubule
- Myelin-associated glycoprotein (MAG), 250, 349, 355–356
- Myosin-II, 216–217
- Myosin-KK, 202
- Myosin Light Chain Kinase (MLCK), 217

- N**
- N-cadherin, 82–83
- NCAM, 24–25
- Ndel1, 297, 298
- NEEP21 (neuron-enriched endosomal protein of 21 kD), 277
- Neogenin, 341
- Nerve growth factor (NGF), 26, 359
- Netrins/Netrin-1
 - axon guidance and, 250
 - commissural axons guidance and, 38–41
 - extracellular cues regulating neuronal polarization, 189–190
 - growth cone cytoskeleton and, 221
 - guidance role described, 2–4
 - mechanisms of axon guidance in the brain and, 148
- Netrin/DCC, integration of guidance information and, 29
- Netrin/DCC, link to activation of guidance receptors, 264
- Netrin/unc6, tropic guidance cues and, 26
- neural cell death and, 339–340
- neuronal migration and, 304
- switching of response after crossing the floor plate, 44–45
- vascular patterning by axon guidance molecules and, 377–378
- Neuregulin-1 (Nrg1), 132, 302
- Neuromuscular junction (NMJ), 330
- Neuronal cell migration guidance
 - cellular interactions in tangential migrations, 301–302
 - chemotaxis in tangential migrations, 302–303
 - classes of neurons in the cerebral cortex, 292–293
 - conclusions and future studies, 305
 - integration of migration and guidance programs within cells, 304–305
 - leading process dynamics, 293–295
 - locomotion, 293
 - migration of guidepost cells, 303–304
 - migration types, 291–292
 - nucleokinesis, 295–298
 - radial glia–neuron interactions, 298–299
 - radial migration regulation, 299–301
- Neuronal guidance
 - conclusions and future studies, 152–153
 - contralateral and ipsilateral tracts in the brain, 149–150
 - development of dopaminergic projections in mouse, 148, 149f
 - human disorders of cranial nerve guidance
 - albinism, 169–170
 - CFOEM1, 170–171
 - Duane retraction syndrome, 171–172
 - Kallmann syndrome, 168–169
 - pontine tegmental cap dysplasia, 172
 - mechanisms of axon guidance in the brain, 146–149
 - mechanistic principles of mammalian brain wiring, 152–153
 - molecular mechanisms controlling neuron targeting, 150–153
 - pioneering axons and brain patterning, 143–146
- Neuronal polarization, 182, 189–190
- Neuronal wiring
 - cell-adhesion molecules, 8–9
 - conclusions and future studies, 11–12
 - cytoskeletal dynamics and guidance cues, 9–11
 - guidance cues diversity
 - ephrins and eph, 6–7
 - experimental approaches to study, 2
 - families of guidance cues, 2
 - netrins and their receptors, 2–4
 - Semaphorins, 4–6
 - Slits, 4
 - guidance-cue signaling beyond neural development, 11
 - morphogens and growth factors, 7–8
- Neuron-enriched endosomal protein of 21 kD (NEEP21), 277
- Neurophilin-1 (Nrp1), 132
 - axon guidance and, 246–248
 - axon pruning and cell death and, 334–335
 - vascular patterning by axon guidance molecules and, 378–379
- Neurotrophin-3 (NT-3), 359
- Neurotrophin-4 (NT-4), 359
- Nfia* (Nuclear factor I genes), 303–304
- NGF (nerve growth factor), 26, 359
- NMJ (neuromuscular junction), 330
- Nogo receptor/Nogo-A
 - axon guidance and, 250
 - axon regeneration and, 354–356
 - synaptogenesis and, 323
- Notch, 260
- Notch pathway, 374
- Nrg1 (Neuregulin-1), 302

Nrp1 (Neurophilin-1), 132
 Nuclear factor I genes (*Nfia*), 303–304
 Nucleokinesis, 293, 295–298
 N-WASP, 243

O

Oculocutaneous albinism (OCA), 169–170
 Odorant receptor (OR). *See* Olfactory system
 Olfactory epithelium (OE), 126.
 See also Olfactory system
 Olfactory sensory neuron (OSN), 126.
 See also Olfactory system
 Olfactory system
 conclusions and future studies, 138
 map formation in *Drosophila*
 axon guidance and dendritic patterning,
 136–138
 development specification of input and output
 neurons, 135–136
 glomerular targeting mechanisms, 135
 map formation in mammals
 activity-dependent refinement, 135
 axonal convergence and topographic mapping,
 130–131
 axon–axon interactions, 132–133
 divergent olfactory signaling mechanisms, 126,
 128–129
 epithelium and bulb correlations, 131–132
 neuronal activity-dependent local axon sorting,
 133–135
 odorant receptor gene choice, 129–130
 OR-instructed glomerular positioning, 132
 sensory neurons and odorant receptor
 proteins, 127f
 spatial organization of olfactory epithelium, 130
 organizational principles, 125–126
 peripheral organization and odorant receptor
 gene choice
 divergent olfactory signaling mechanisms,
 126, 128–129
 odorant receptor gene choice, 129–130
 sensory neurons and odorant receptor
 proteins, 126, 127f
 spatial organization, 130
 Omgp (oligodendrocyte myelin glycoprotein), 250,
 349, 355–356
 Optic tectum (OT), 106
 Orbit/MAST, 222, 225
 Outer plexiform layer (OPL), 75

P

p27Kip1, 295
 p35/39, 297–298, 299
 Pak1, 295

PAR3-PAR6-aPKC, 184–185
 Par4 and Par1 orthologs. *See* LKB1
 Patched, 341
 PCD (programmed cell death), 330
 Pea3, 65
 Peripheral nervous system (PNS), 331
 PGC (preganglionic motor column), 54f
 Phosphatase and Tensin (PTEN), 186
 PI3K (phosphatidylinositol-3 kinase), 185–186,
 240–242
 Pinceaux formations, 151
 Pioneer neurons, 16, 18, 19f, 143–146
 PirB, 356
 PKA (protein kinase A), 208, 268–269
 Plasma membrane ganglioside sialidase (PMGS), 242
 Plexins/Plexin A, 27
 axon guidance and, 246–248
 axon pruning and cell death and, 334–335
 growth cone cytoskeleton and, 219
 guidance role described, 5–6
 link to activation of guidance receptors, 264
 synaptogenesis and, 324
 vascular patterning by axon guidance molecules
 and, 378–379
 Plus-end-tracking proteins (+TIPs), 222, 225
 PMGS (plasma membrane ganglioside sialidase), 242
 PNS (peripheral nervous system), 331.
 See also Axon regeneration
 PNs (projection neurons). *See also* Olfactory system
 Pontine neurons, 295
 Pontine tegmental cap dysplasia (PTCD), 172
 Preganglionic motor column (PGC), 54f
 Profilin, 219–220
 Programmed cell death (PCD), 330
 Projection neurons (PNs), 132. *See also* Olfactory system
 Protein kinase A (PKA), 208, 268–269
 Protein kinase B, 186
 Proteolytic processing and receptor signaling,
 259–260
 Pruning and cell death. *See* Axon pruning and
 cell death
 PTCD (pontine tegmental cap dysplasia), 172
 PTEN (Phosphatase and Tensin), 186
 Pyramidal cells, 292. *See also* Neuronal cell migration
 guidance

R

R1-R6 neurons, 97
 Rac isoform, 251, 264
 Radial glia cells, 298–299
 RAF/MEK/ERK, 187–188
 RAGS (repulsive axon guidance signal), 107
 Receptor protein tyrosine phosphatases (RPTPs), 358
 Receptor tyrosine kinases (RTKs), 379–380
 Reelin, 84, 299–301

- Regeneration of axons. *See* Axon regeneration
Repulsive axon guidance signal (RAGS), 107
Repulsive Guidance Molecule (RGM), 341
Retina. *See* Lamina-specific axon targeting
Retinal axons, 16
Retinal ganglion cells (RGCs), 76–77, 92,
94–96, 333
Retinoic acid receptor, 333
RGM (Repulsive Guidance Molecule), 341
Rho and Ras GTPases
axon branching, 251–252
axon growth, 243–245
axon guidance
ephrins, 248–250
other guidance cues, 250–251
Rac pathways and, 245–246
Semaphorins and, 246–248
axon initiation
GSK-3 phosphorylation and inhibition, 242
loss-of-function studies, 243
neuronal polarization model, 240–242
Rac-mediated phosphorylation, 242–243
conclusions and future studies, 252
GTPases cycle, 239–240
guidance molecules and, 10–11
guidance receptors link to activation of
ephrins and eph forward signaling, 265–266
ephrins and eph reverse signaling, 266–267
kinase cascades, 267–268
Netrin-DCC, 264
Semaphorin3A-Plexin, 264–265
Slit-Robo, 267
upstream regulatory role, 268–269
signaling pathways involved in axon initiation and
growth, 185
RIA, 315
Rictor, 100
Rnd1/2/3, 248
Robo-3/Rig-1, 29
Robo family/Robo1
actin-associated proteins in axon guidance, 207
axon guidance and, 250
ipsilateral or contralateral pathway choice and,
41–44
longitudinal pathways formation and, 47–48, 49f
mechanisms of axon guidance in the brain and,
148, 285
neuronal migration and, 303
vascular patterning by axon guidance molecules
and, 375–377
ROCK, 242, 243, 246–248
Rohon-Beard neurons, 96, 97
Roundabouts. *See* Robo family/Robo1
RPTPs (receptor protein tyrosine phosphatases), 358
R-Ras GAP-related domain, 248
RTKs (receptor tyrosine kinases), 379–380
RTN4a/Nogo-A, 349
Ryk, 353
- ## S
- SAC (stratum album centrale), 77
SAD-A/B, 183–184
SC (superior colliculus), 106
SDF1, 26
Sdk1 (Sidekick), 81
Sdk2, 81
Sema3Neuropilin signaling, 64
Semala (Fas IV), 48
Semaphorins/Semaphorin1a/3A, 27
axon guidance and, 246–248, 284
axon guidance receptors signaling and, 259
axon pruning and, 334–335
axon regeneration and, 352–353
extracellular cues regulating neuronal
polarization, 190
growth cone cytoskeleton and, 219, 221, 226
guidance role described, 4–6
link to activation of guidance receptors, 264–265
in mammalian olfactory system, 132, 133
mechanisms of axon guidance in the brain
and, 148
neural cell death and, 340
neuronal migration and, 303, 304
switching of response after crossing the floor plate,
44–45
synaptogenesis and, 320, 324
tropic guidance cues and, 26
vascular patterning by axon guidance molecules
and, 378–379
SFGS (stratum fibrosum et griseum superficiale), 77
SFKs (Src family kinases), 267–268
SGC (stratum griseum centrale), 77
Shh (Sonic Hedgehog), 7, 47, 144, 341
Sidekick (Sdk1), 81
Signaling from axon guidance receptors
activation of Rho GTPases
ephrins and eph forward signaling,
265–266
ephrins and eph reverse signaling, 266–267
kinase cascades, 267–268
Netrin-DCC, 264
Semaphorin3A-Plexin, 264–265
Slit-Robo, 267
upstream regulatory role, 268–269
calcium and, 261–262
conclusions and future studies, 269
cyclic nucleotides and, 262–263
endocytosis, 257–259
proteolytic processing and receptor signaling,
259–260
second messengers and, 261

- Sin1, 100
- Slit
- axon guidance and, 250
 - guidance role described, 4
 - ipsilateral or contralateral pathway choice and, 41–44
 - mechanisms of axon guidance in the brain and, 148, 285
 - Slit-Robo link to activation of guidance receptors, 267
 - vascular patterning by axon guidance molecules and, 375–377
- SM-216289, 352–353
- SO (stratum opticum), 77
- Sonic Hedgehog (Shh), 7, 47, 144, 341
- Spastin, 226–227
- Spectrin, 216
- SPV (stratum periventriculare), 77
- Src family kinases (SFKs), 267–268
- SRF-dependent transcription, 213
- STARS, 213
- Stratum album centrale (SAC), 77
- Stratum fibrosum et griseum superficiale (SFGS), 77
- Stratum griseum centrale (SGC), 77
- Stratum opticum (SO), 77
- Stratum periventriculare (SPV), 77
- Subventricular zone (SVZ), 293
- Superior colliculus (SC), 106
- Synaptic matchmaking. *See* Lamina-specific axon targeting
- Synaptogenesis
- axon guidance and, 312, 314
 - conclusions and future studies, 325
 - contact stabilization, 318
 - filopodial motility, 316
 - filopodial motility, BDNF/TrkB, 316–317
 - filopodial motility, EphB2, 318
 - neuronal synaptic plasticity and, 311–312, 313f
 - Semaphorins general role, 320
 - synapse plasticity and
 - BDNF/TrkB, 321–322
 - ephrins and eph, 322–323
 - Nogo receptor, 323
 - overview, 320–321
 - Semaphorins and Plexins, 324
 - Wnt proteins, 324
 - synaptic maturation, 318–320
 - synaptic pre patterning, 314–316
 - synaptic scaling, 324–325
- Synkinesis, 161–162
- Tenascin-C/R, 84
- Terminal synapses, 314
- Termination zone (TZ), 111
- TGF- β , 7, 324–325
- TGN, 276–277
- Thalamocortical axons (TCAs), 304
- Tiling mechanism. *See* Dendrite and axon spacing mechanisms
- Tip cell concept, 373–374
- +TIP proteins (plus-end-tracking), 222, 225
- Topographic mapping
- chemoaffinity principle, 73–74
 - in fish, 107–109
 - large-scale stereotyped pruning in, 333
 - olfactory system, 130–131
 - visual system (*see* Visual map development)
- TORC2 (target of rapamycin complex 2), 100
- Tract of the postoptic commissure (TPOC), 144
- Trafficking guidance receptors
- conclusions and future studies, 285–286
 - L1/NgCAM and
 - axonal enrichment of receptors role, 276
 - control of guidance receptor distribution at growth cones and, 282–284
 - transcytosis and, 277–278
 - membrane traffic's role in guidance and function of neurons, 273–274
 - neuronal-specific polarized system
 - neuronal adaptations to endosomal system, 275–276
 - neuronal adaptations to secretion, 275
 - pathways to axons
 - axonal targeting by selective endocytosis/retention, 278–280
 - biosynthetic sorting in the TGN, 276–277
 - indirect polarized delivery by transcytosis, 277–278
 - receptor distribution mechanisms, 274
 - regulation of diffusibility, 280–282
 - regulation of local diffusibility, 284–285
 - regulation of local endocytosis, 283–284
 - regulation of local insertion, 282–283
- Transcytosis, 277–278
- Tricornered (*trc*), 100
- Tropomyosin-related kinase B (TrkB), 316–317
- Turtle (*Tutl*), 93, 99
- Type III Nrg1 (CRD-Nrg1), 302
- Type I/II Nrg1 (Ig-Nrg1), 302
- Tyrosine phosphatase, 93
- TZ (termination zone), 111
- T**
- TAG-1, 259
- Target of rapamycin complex 2 (TORC2), 100
- TCAs (thalamocortical axons), 304
- U**
- Unc family/UNC-5
- actin-associated proteins in axon guidance, 207–208
 - axon guidance and, 250

- axon guidance receptors signaling and, 259
 - neural cell death and, 339–340
 - UNC-44, 216
 - UNC-115/ablim, 212–213
 - UNC-6/netrin and synaptogenesis, 314–315
 - vascular patterning by axon guidance molecules and, 377–378
- V**
- VAMP, 283
 - Vascular endothelial growth factor A (VEGF-A), 370.
See also Vascular patterning
 - Vascular patterning
 - angiogenic growth of blood vessels, 371–372
 - axon guidance molecules and, 374–375
 - ephrins and eph, 379–381
 - Netrins and UNC-5, 377–378
 - Semaphorins, Plexins, and Neuropilins, 378–379
 - Slits and Robos, 375–377
 - conclusions and future studies, 381
 - tip cell concept, 373–374
 - vascular system described, 369–371
 - Vascular smooth muscle cells (vSMCs), 370
 - Vav family, 257–259
 - VEGF-A (vascular endothelial growth factor A), 370.
See also Vascular patterning
 - Veils, 200
 - Ventral cephalic sheath cells (VCSCs), 315
 - Ventricular zone (VZ), 291
 - Vertebrates
 - mammals (*see* Mammals (mice))
 - midline cells and axonal guidance (*see* Midline cells)
 - stages of visual map development, 107–109
 - Visual map development
 - anterior-posterior mapping molecule
 - candidate, 120
 - chemoaffinity hypothesis, 106–107
 - conclusions and future studies, 120–121
 - dorsal-ventral mapping, 116–118
 - eph and ephrins system
 - bifunctional and bidirectional signaling, 109
 - contributions to forming functional maps, 119–120
 - control of dorsal-ventral mapping, 117–118
 - interstitial branching, 115–116
 - temporal-nasal to anterior-posterior mapping, 109–113
 - lamina-specific axon targeting in the visual system, 75–77
 - model for mapping, 116
 - neural activity-dependent mechanisms, 118–120
 - stages of, 107–109
 - topographic guidance activities identification, 107
 - topographic mapping of the visual system, 105–106
 - topographic-specific interstitial branching, 113–116
- VLDLR, 299–301
- VZ (ventricular zone), 291
- W**
- Wallerian degeneration, 330, 333–334
 - Wnt proteins
 - anterior-posterior guidance decisions and, 46
 - axon guidance and, 7
 - axon regeneration and, 353
 - extracellular cues regulating neuronal polarization, 189–190
 - neuronal guidance and, 144
 - synaptogenesis and, 319–320, 324
 - Wnt4, 27
- X**
- Xenopus*, 261–262, 263
- Y**
- YRSLE, 277–278, 284
- Z**
- Zebrafish, 77–79