

Preface

SINCE THE DISCOVERY OF GLIAL CELLS AS a major class of cells in the nervous system more than 100 years ago, their functions have been the subject of great mystery and debate. Glial cells are generally considered to consist of all neuroectoderm-derived cell types that are not electrically excitable neurons. Glia are present in both invertebrates and vertebrates, and according to most estimates they constitute the majority of cells in the mammalian nervous system.

But what do glial cells do? Progress had been limited by a lack of tools to identify and genetically manipulate them, to purify and culture them, and to study their physiology. Although there is much more work to be done, profound technical advances over the past 30 years have finally made it possible to begin to really understand glial development and function.

Our goal in this monograph is to review recent progress in our understanding of the major classes of glial cells: astrocytes, oligodendrocytes, Schwann cells, microglia, as well as invertebrate glia. How are they generated, how do they develop, and what are their functions both normally and in disease?

We review this progress in seven main book sections. In Section 1, we consider the types of glial cells and their functions in worms, flies, and fish, which have all emerged as powerful new genetic model systems for understanding glial cell function. Diverse aspects of glial biology, from astrocyte specification, growth and function, to axon–glia interactions and glial phagocytic functions are well conserved in these animals, and can be subjected to powerful forward- and molecular-genetic approaches to characterize conserved glial signaling pathways.

Next, in Section 2, we cover astrocytes. Chapters in this section review their development and regional specialization. They also review their surprisingly active roles in synapse formation, function, plasticity, and elimination, as well as in controlling blood flow. Intracellular pathways involved in calcium signaling and metabolism differ strikingly in astrocytes compared to neurons; several chapters review these differences and their possible functional implications. Last, the roles of reactive astrocytes and their roles in central nervous system (CNS) disease are considered.

In Sections 3 and 4, we review progress in understanding the biology of myelinating glial cells and their precursors, beginning with oligodendrocyte precursor cells (OPCs), and also covering oligodendrocytes and Schwann cells. Our knowledge of functional roles for OPCs has been expanding rapidly beyond simply their ability to make new oligodendrocytes, and now includes their shaping of neural circuits. Oligodendrocyte generation continues into adulthood, in which these cells may play important roles in adaptive myelination and even certain kinds of learning. An enormous amount has been learned about how myelinating cells are specified and how they myelinate axons, but also how they then support axonal function. Several chapters review how oligodendrocytes and Schwann cells help to organize nodal, paranodal, and internodal axon domains, which is critical for rapid and faithful electrical conduction of action potentials. As for astrocytes in the CNS, Schwann cells are now known to have multiple active roles in the control of synapse formation and function in the peripheral nervous system (PNS). Roles for perisynaptic Schwann at the neuromuscular junction are discussed, along with how Schwann cells help orchestrate nerve assembly and repair.

In Sections 5 and 6, we review the exciting recent progress on the origin and functions of microglia and other neuroimmune interactions mediated by glia at the boundaries of neuronal and non-neuronal tissues. Section 5 begins with an introduction to microglial roles in coordinating CNS neuroimmune function and in the spatial patterning and synaptic wiring throughout the healthy, developing, and adult CNS; additional roles for microglia are discussed in chapters throughout the book. Section 6 goes on to explore how glia play roles in forming barriers or regulating peripheral

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function, ranging from the blood–brain barrier to the long-overlooked satellite glial cells found in peripheral ganglia and enteric glia that support neuronal function in internal organs. The morphology and function of glia at CNS–PNS transition zones are also considered, along with the cellular and functional basis of the glymphatic and lymphatic waste-clearance system in the brain and its potential roles in disease.

Finally, in Section 7, we consider recent studies that implicate glial cells as critical players in diverse aspects of disease, repair, and regeneration. Chapters focus on the critical roles of glial cells in promoting and hindering axon regeneration after injury in the PNS and CNS. Included is a discussion of the recent explosion of exciting work revealing the likely origin of and neuronal regulatory roles in driving glial malignancies such as glioma. This is followed by a discussion of the biology of how astrocytes and microglia might help or hinder (or both) in neurodegenerative disease. The book closes with chapters exploring demyelinating diseases in the CNS and PNS, white matter disorders, and diseases of the peripheral nerve.

What emerges from this work is new insight into the importance of glial cells, especially an appreciation that the development, function, and malfunction of our brains can only be understood as a signaling interplay between neurons and glial cells. Rather than being passive support cells as long thought, glial cells are highly active participants in the vast majority, if not all, neurobiological processes. In complex animals, there is very little that neurons do without talking to glia.

Equally important, this monograph highlights the reality that many mysteries remain. Trainees considering entering the field should be excited by the vast open space to be explored, key challenges to be overcome on our journey, and complex functional roles to be demystified. To name just a few: how do glia keep neurons alive, what is the overall role of glia in circuit function, what neuroactive substances do glia secrete and how do they regulate neuronal function, have human astrocytes evolved in their abilities to control synapse formation or function, and does that contribute to the enhanced cognitive capacities of humans? What is the functional significance of regional astrocyte specialization, do astrocytes function individually or as a syncytium (or both), what other unexpected functions do oligodendrocyte lineage cells have beyond myelination, what exactly are the roles of microglia in health and disease, and could glial cells be important targets for new drugs? Clearly there is much work left to be done! Our hope is that readers of this book will be stimulated to join the chase.

We wish to thank the staff of Cold Spring Harbor Laboratory Press, namely (the ever-so-patient), Barbara Acosta for inviting us to edit this volume and managing the project, and Editorial Assistant Danett Gil and Production Editor Diane Schubach for all their hard work in producing this volume. For the cover photographs, we are indebted to Jiakun Chen (UNC) and Cody Call (OHSU) for their beautiful images. Last, we thank all of the authors for their superb contributions to this volume, and for their patience with the many Covid-related and other delays we experienced along the way.

Finally, we want to close by acknowledging two colleagues we recently lost far too soon. Laura Feltri (MD) was a widely respected neuroscientist and mentor, whose research focused on peripheral nerves, Charcot-Marie-Tooth disease, and multiple sclerosis. Laura died December 25, 2023. She made a number of seminal discoveries in the area of myelination, many of which were in collaboration with her husband, Lawrence Wrabetz (MD). Laura was a fixture at meetings, and was a pioneer in pushing creative and difficult molecular-genetic approaches to explore the molecules that regulate myelin biology. Her approach to hard questions was relentless and rigorous. Laura was a member and then-chair of the National Institutes of Health (NIH) study section on the Cellular and Molecular Biology of Glia, President of the Peripheral Nerve Society, an AAAS fellow, and a guiding voice for many scientific organizations, including the Muscular Dystrophy Association and the National Multiple Sclerosis Society. It is hard to think of a kinder, friendlier face one might bump into at a meeting, and then have a remarkably stimulating discussion with. She is sorely missed.

The first edition of this book, like many things in our field (e.g., the CSHL Glia in Health and Disease Meeting), was the product of Ben Barres' (MD/PhD) passion for the field of glial biology,

dedication to academic science, and his desire to bring trainees and faculty together for meaningful scientific discussion. Ben studied nearly all corners of glial cell biology during his career—astrocyte development and function, OPCs, myelin biology, and microglia. He died on December 27, 2017 at the age of 63. It is hard to imagine any contemporary researcher that had a greater impact on the field of glial biology, from his own scientific breakthroughs, to his relentless mentoring of his trainees (and anyone else within earshot), to his remarkably tuned moral compass and outspoken nature on social issues. Ben made a lasting impact on the quality of our science, and how we treat each other in the scientific community through his efforts. This continues through his own trainees and friends still working in our field. He was a bright light that is sorely missed. Amazingly, he had all of his massive impact having only had a laboratory for ~24 years.

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