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COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.org

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A Subject Collection from *Cold Spring Harbor Perspectives in Biology*
Articles online at www.cshperspectives.org

Printed in the United States of America

Executive Editor	Richard Sever
Managing Editor	Maria Smit
Senior Project Manager	Barbara Acosta
Permissions Administrator	Carol Brown
Production Editor	Diane Schubach
Production Manager/Cover Designer	Denise Weiss
Publisher	John Inglis

Front cover artwork: Protoplasmic astrocyte (red) of the adult rat hippocampus filled with the fluorescent dye Lucifer yellow and imaged by confocal microscopy. The astrocyte contacts nearby blood vessels (green) labeled with DiI. (Image courtesy of Eric Bushong and Mark Ellisman, University of California, San Diego, La Jolla, California.)

Library of Congress Cataloging-in-Publication Data

Glia (Barres)
Glia / edited by Ben A. Barres, Marc R. Freeman and Beth Stevens.
p. ; cm.
"A subject collection from Cold Spring Harbor perspectives in biology."
Includes bibliographical references and index.
Summary: "Glia are cells that serve to nourish and support the neuronal cells that relay electrical signals through the nervous system. They also play critical roles in development and synapse formation, helping to establish neural circuits. This book examines our understanding of the basic biology of glia and their roles in diseases such as Alzheimer's and cancer"--Provided by publisher.
ISBN 978-1-62182-027-7 (hardcover : alk. paper)
I. Barres, Ben, editor. II. Freeman, Marc R., 1970- , editor. III. Stevens, Beth, 1970- , editor. IV. Cold Spring Harbor perspectives in biology. V. Title.
[DNLM: 1. Neuroglia--Collected Works. WL 102]

QP363.2
612.8′1046--dc23
2014039908
10 9 8 7 6 5 4 3 2 1

All World Wide Web addresses are accurate to the best of our knowledge at the time of printing.

For a complete catalog of all Cold Spring Harbor Laboratory Press publications, visit our website at www.cshlpress.org.

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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, perhaps as many as 65% of cells in the mouse brain and 80% in the human brain. (Some investigators have estimated that they may constitute >90% of the cells in very large brains [e.g., in whales and elephants].)

But what do they do? Progress has long been limited by lack of tools to identify and genetically manipulate them, to purify and culture them, and to study their physiology. Although, to be sure, there is much more work to be done, profound technical advances over the past 20 years have finally made it possible to begin to make great inroads in our understanding of glial development and function. Our goal in this monograph is to review this recent progress in our understanding of the major classes of glial cells: astrocytes, oligodendrocytes, Schwann cells, microglia, and 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 six main book sections. In Section 1, we review our current understanding of astrocytes. Chapters in this section review the development of astrocytes and the recent discovery that they are regionally specialized. These chapters also review surprisingly active roles of astrocytes 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 functions. Last, the roles of astrocytes at the blood–brain barrier and reactive astrocytes and their roles in disease are considered.

Next, in Sections 2 and 3, we review progress in understanding of the myelinating glial cells, oligodendrocytes and Schwann cells. Much has recently been learned about how myelinating cells are specified and how they myelinate axons. Moreover, recent studies reveal that oligodendrocyte generation continues into adulthood, where it may even have an important role in certain kinds of learning. Several chapters review how oligodendrocytes and Schwann cells help to organize nodal, paranodal, and intermodal axon domains, which is critical for rapid and faithful electrical conduction of action potentials. And as for astrocytes in the central nervous system (CNS), Schwann cells have also emerged as having many active roles in the control of synapse formation and function in the peripheral nervous system (PNS).

In Section 4, we review the exciting recent progress in our understanding of the origin and functions of microglia. In Section 5, 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. Finally, in Section 6, we consider recent studies that implicate glial cells as critical players in 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, respectively, on recent work demonstrating that glia are active contributors to neuronal death in neurodegenerative diseases, and on the mystery of why CNS remyelination fails to occur after injury.

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 of, if not all, neurobiological processes. But equally emerging from a reading of these chapters is an appreciation that many mysteries remain. To name just a few: How do astrocytes keep neurons alive, what is the overall role of astrocytes 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 oligodendrocytes have undiscovered functions other than 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, Richard Sever for inviting us to edit this volume and project manager Barbara Acosta and production editor Diane Schubach for all their hard work in producing this volume. For the cover photograph, we are indebted to Eric Bushong and Mark Ellisman at University of California at San Diego. Last, we thank all of the authors for their superb contributions to this volume.

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