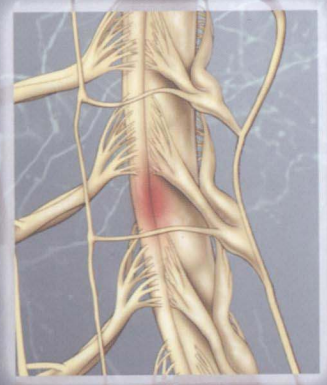
NEURAL REGENERATION

神经再生

KWOK-FAI SO, XIAO-MING XU



SCIENCE PRESS

NEURAL REGENERATION

Edited by

KWOK-FAI SO

XIAO-MING XU

Science Press
Beijing

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
225 Wyman Street, Waltham, MA 02451, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

ISBN:978-7-03-044098-3

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-12-801732-6

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

Typeset by TNQ Books and Journals
www.tnq.co.in

Printed and bound in the United States of America

NEURAL REGENERATION

List of Contributors

Larry I. Benowitz Laboratories for Neuroscience Research in Neurosurgery and F.M. Kirby Neurobiology Center, Children's Hospital Boston, Boston, MA, USA; Departments of Surgery and Ophthalmology and Program in Neuroscience, Harvard Medical School, Boston, MA, USA

John L. Bixby The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, FL, USA; Center for Computational Sciences, University of Miami Miller School of Medicine, Miami, FL, USA; Department of Neurological Surgery, University of Miami Miller School of Medicine, Miami, FL, USA; Department of Molecular & Cellular Pharmacology, University of Miami Miller School of Medicine, Miami, FL, USA

Todd J. Brown Research and Development Service, Richard L. Roudebush VA Medical Center, Indianapolis, IN, USA; Department of Anatomy & Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA

Qi Lin Cao The Vivian L Smith Department of Neurosurgery, University of Texas Health Science Center at Houston, Houston, TX, USA; Center for Stem Cell and Regenerative Medicine, The Brown Foundation Institution of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA

Dong Feng Chen Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA; VA Boston Healthcare System, Boston, MA, USA

Justin Chew Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Kin-Sang Cho Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Samuel David Centre for Research in Neuroscience, The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Lingxiao Deng Spinal Cord and Brain Injury Research Group, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Neurological Surgery and Goodman and Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA

Fei Ding Jiangsu Key Laboratory, Nantong University, Nantong, Jiangsu, P.R. China

Sarah A. Dunlop Experimental and Regenerative Neurosciences, School of Animal Biology, University of Western Australia, Crawley, Australia

Keith N. Fargo Research and Development Service, Edward Hines, Jr. Department of Veterans Affairs Hospital, Hines, IL, USA; Department of Molecular Pharmacology and Therapeutics, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; Alzheimer's Association, National Office, Chicago, IL.

Toby A. Ferguson Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA

Eileen M. Foecking Department of Otolaryngology-Head and Neck Surgery, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; Research and Development Service, Edward Hines, Jr. Department of Veterans Affairs Hospital, Hines, IL, USA

Qing-Ling Fu Otorhinolaryngology Hospital, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Mary Pauline Galea Department of Medicine, The University of Melbourne, VIC, Australia

Cédric C. Geoffroy Department of Neurosciences, University of California San Diego, La Jolla, California, USA

Shu-chao Ge National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Chenying Guo Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Jiasong Guo Department of Histology and Embryology, Southern Medical University, Guangzhou, China; Key Laboratory of Tissue Construction and Detection of Guangdong Province, Guangzhou, China; Institute of Bone Biology, Academy of Orthopedics, Guangdong Province, Guangzhou, China

Xiaosong Gu Jiangsu Key Laboratory, Nantong University, Nantong, Jiangsu, P.R. China

Theo Hagg Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN, USA

Cheng He Institute of Neuroscience and Key Laboratory of Molecular Neurobiology of Ministry of Education, Neuroscience Research Center of Changzheng Hospital, Second Military Medical University, Shanghai, China

Zhigang He F.M. Kirby Neurobiology Center, Children's Hospital; Department of Neurology, Harvard Medical School, Boston, MA, USA

John D. Houle Department of Neurobiology and Anatomy and Drexel Spinal Cord Research Center, Drexel University College of Medicine, Philadelphia, PA, USA

Yu-bin Huang National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Bing Hu National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Lyn B. Jakeman Department of Physiology and Cell Biology, Center for Brain and Spinal Cord Repair, The Ohio State University College of Medicine, Columbus, OH, USA

Kathryn J. Jones Research and Development Service, Richard L. Roudebush VA Medical Center, Indianapolis, IN, USA; Department of Anatomy & Cell Biology, Indiana University School of Medicine, Indianopolis, IN, USA

Yoshiki Koriyama Graduate School and Faculty of Pharmaceutical Sciences, Suzuka University of Medical Science, Suzuka, Japan; Laboratories for Neuroscience Research in Neurosurgery and F.M. Kirby Neurobiology Center, Children's Hospital Boston, Boston, MA, USA; Departments of Surgery and Ophthalmology and Program in Neuroscience, Harvard Medical School, Boston, MA, USA

Antje Kroner Centre for Research in Neuroscience, The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Daniel H.S. Lee Department of Anatomy, Faculty Medicine, University of Hong Kong, Hong Kong, China

Vance P. Lemmon The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, FL, USA; Center for Computational Sciences, University of Miami Miller School of Medicine, Miami, FL, USA; Department of Neurological Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Shuxin Li Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA

Jie Liu Jiangsu Key Laboratory, Nantong University, Nantong, Jiangsu, P.R. China

Ahmed Moghieb Center for Neuroproteomics & Biomarkers Research, Department of Psychiatry, University of Florida, Gainesville, FL, USA; Department of Chemistry, University of Florida, Gainesville, FL, USA

Paul J. Reier Department of Neuroscience, University of Florida College of Medicine, Gainesville, FL, USA

Jennifer Rodger Experimental and Regenerative Neurosciences, School of Animal Biology, University of Western Australia, Crawley, Australia

Michael E. Selzer Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA; Department of Neurology, Temple University School of Medicine, Philadelphia, PA, USA

Dale R. Sengelaub Department of Psychological and Brain Sciences and Program in Neuroscience, Indiana University, Bloomington, IN, USA

Kartavya Sharma Department of Neurology, UT Southwestern Medical Center, Dallas, TX, USA

Michael I. Shifman Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA

George M. Smith Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA

Kwok-Fai So GHM Institute of CNS Regeneration, Jinan University, Guangzhou, P.R. China; Department of Ophthalmology, and State Key Laboratory of Cognitive and Brain Sciences, The University of Hong Kong, Hong Kong, P.R. China

Huanxing Su Department of Anatomy, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China; State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao SAR, China

Zhida Su Institute of Neuroscience and Key Laboratory of Molecular Neurobiology of Ministry of Education, Neuroscience Research Center of Changzheng Hospital, Second Military Medical University, Shanghai, China

Chen Tian National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Veronica J. Tom Department of Neurobiology and Anatomy and Drexel Spinal Cord Research Center, Drexel University College of Medicine, Philadelphia, PA, USA

Chandler Walker Spinal Cord and Brain Injury Research Group, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Neurological Surgery and Goodman and Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA

Kevin K.W. Wang Center for Neuroproteomics & Biomarkers Research, Department of Psychiatry, University of Florida, Gainesville, FL, USA; Department of Neuroscience, University of Florida, Gainesville, FL, USA; Taipei Medical University, Taipei, Taiwan, China

Xiaofei Wang Spinal Cord and Brain Injury Research Group, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Neurological Surgery and Goodman and Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA

Wutian Wu Department of Anatomy, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China; State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Macao, China; Institute of Chinese Medical Sciences, University of Macau, Macao SAR, China; Institute of CNS Regeneration, Jinan University and The University of Hong Kong, Guangzhou, China

Xiao-Ming Xu Spinal Cord and Brain Injury Research Group, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Neurological Surgery and Goodman and Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA

Yumin Yang Jiangsu Key Laboratory, Nantong University, Nantong, Jiangsu, P.R. China

Wu Yin National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Wise Young Department of Cell Biology & Neuroscience, W.M. Keck Center for Collaborative Neuroscience, Piscataway, NJ, USA

Juliet C. Yuan Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Qiuju Yuan Department of Anatomy, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

Guixin Zhang Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, Philadelphia, PA, USA

Zhiqun Zhang Center for Neuroproteomics & Biomarkers Research, Department of Psychiatry, University of Florida, Gainesville, FL, USA

Binhai Zheng Department of Neurosciences, University of California San Diego, La Jolla, California, USA

Lihua Zhou Department of Anatomy, Zhong Shan School of Medicine, Sun Yat-Sen University, Guangzhou, China

Ruilin Zhu Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA, USA; Department of Ophthalmology, Peking University First Hospital, Beijing, China

Su-qi Zou National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, China

Yimin Zou Neurobiology Section, Biological Sciences Division, University of California, San Diego, CA, USA

Contents

V

TRANSPLANTATION-MEDIATED NEURAL REGENERATION

SECTION I

INTRODUCTION

CHAPTER

1

Advances and Challenges for Neural Regeneration Research

Xiaofei Wang[1,2], *Kwok-Fai So*[4,5], *Xiao-Ming Xu*[1,2,3]

[1]Spinal Cord and Brain Injury Research Group, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Neurological Surgery and Goodman and Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA; [4]GHM Institute of CNS Regeneration, Jinan University, Guangzhou, P.R. China; [5]Department of Ophthalmology, and State Key Laboratory of Cognitive and Brain Sciences, The University of Hong Kong, Hong Kong, P.R. China

1. NERVOUS SYSTEM, NERVE INJURY, AND NEURAL REGENERATION

The nervous system is divided into two parts: the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS), which consists of cranial and spinal nerves along with their associated ganglia. The function of the CNS and PNS is to relay information to and from all parts of the body. This communication is made possible through an extensive network of neurons and supporting cells called glia, including astrocytes, oligodendrocytes, and microglia.

Nerve injury, whether traumatic or degenerative, disrupts the normal flow of information and can, depending on the location and mechanism of injury, lead to deleterious effects. Injury or sudden trauma, such as from automobile accidents, falls, sports-related activities, etc., can cause nerve fibers or axons to be partially or completely severed, crushed, compressed, or stretched. When an axon is damaged, the distal segment undergoes Wallerian degeneration, losing its myelin sheath [1]. The axotomized neurons either die by necrosis or apoptosis or undergo a chromatolytic reaction, which is an attempt to repair. Injury to the nervous system also triggers the responses of glial cells, including oligodendrocytes, astrocytes, and microglia in the CNS; Schwann cells (SCs) in the PNS; and blood-derived macrophages that participate in both CNS and PNS injury processes. The responses of these cells to injury include cell death, proliferation, migration, and production of inflammatory mediators and growth factors, thus influencing processes of axonal degeneration and regeneration. Thus, nervous system injuries affect not only neurons and their processes but also glial cells.

Neural regeneration refers to the regrowth or repair of nervous tissues, cells, or cell products. Such mechanisms may include generation of new tissues, neurons, glia, axons, myelin, or synapses. Beyond the common knowledge of neurogenesis, a wider concept of neural regeneration may comprise endogenous neuroprotection leading to neuroplasticity and neurorestoration. Neural regeneration can also be promoted by implantation of viable tissues or cells. Neural regeneration differs between the PNS and the CNS owing to different neuronal and glia responses to injury as well as the different environments that the regenerative axons and cells encounter.

2. TECHNOLOGICAL ADVANCES IN NEURAL REGENERATION RESEARCH

2.1 Models

Preclinical animal models are critical for understanding regenerative neurobiology and for testing treatment strategies prior to implementation in clinical practice. For regeneration research, in vitro, ex vivo, or in vivo models, described below, have been used extensively and complementarily.

Neural Regeneration
http://dx.doi.org/10.1016/B978-0-12-801732-6.00001-X

2.1.1 *In vitro Model*

The flexibility and ease of control offered by the in vitro model make it a useful tool for the study of neural regeneration. Glass micropipettes can be used to sever processes from cultured neurons or tissue explants to study axonal and dendritic regrowth in vitro [2–4]. Although this method can cut many axon segments simultaneously, it cannot be used to isolate axon and dendritic segments. Fine knife cutting is another localized physical injury, which can precisely cut neurites [5,6]; this method, however, damages the coated substrate and sets up an artificial sulcus, which may prevent the truncated neurite from regrowing. Microdissection of a neurite with a laser beam offers more precise control [7,8] that provides a unique platform for regeneration research [9]. A nanocutting device with a cutting edge of less than 20 nm radius of curvature was developed that enables high-precision microdissection and subcellular isolation of neuronal structures [10]. With these devices, not only can a single-axon transection model be established, but also regeneration-related functional components of neurons, such as segments of axons, dendrites, dendritic spines, and nodes of Ranvier, can be isolated in culture.

2.1.2 *Ex vivo Model*

An ex vivo model is ethically advantageous, requires no postsurgical animal care, enables more reproducibility between lesions, and provides a tightly controlled artificial environment for regeneration studies. Published ex vivo spinal cord models include the culture of several hundred micrometers-thick transverse slices maintained for up to three weeks [11], unfixed longitudinal cryostat sections of spinal cord maintained for one week [12], and a novel ex vivo model that enables the culture of intact postnatal spinal cord segments for up to five days and the assessment of peripheral nerve grafting repair [13].

2.1.3 *In vivo Model*

Although invertebrates and lower vertebrates, such as *Caenorhabditis elegans* [14–16], lamprey [17–19], zebrafish [20–23], and lizard [24,25], have long been applied for neural regeneration research, the rat sciatic nerve, brain, and spinal cord injury models have been the most commonly used for studies of neural regeneration. Rodent models, such as rats and mice, are economical compared to large-animal models and primates, simple to handle and care for, very resistant to surgical infections, and can be investigated in large groups. Rodent models can be used for electrophysiology, functional recovery, muscle and nerve morphology, and other assessments of nerve regeneration [26,27]. The major value of the mouse model is the ability to answer mechanistic neural regeneration questions [28,29]. The rabbit, dog, and cat are large-animal species more frequently used for peripheral and central nervous system injury research. Large mammals such as sheep [30,31], pigs [32,33], and monkeys [34–37] have increasingly been employed to study neural regeneration. These large species are limited by extremely high costs related to animal care, the narrow range of assessments available, and the complexity of training for functional testing. Transgenic animals, particularly mice, that express fluorescent proteins in specific neuronal subsets provide potentially powerful tools for the study of neural regeneration. One strategy involves expressing fluorescent proteins under the control of neuron-type-specific promoters [38]. Another approach involves the use of bacterial artificial chromosome (BAC) mice [39,40]. Genetic labels can provide specificity in axonal labeling that is hypothetically independent of tracer transport [41]. Moreover, BAC mice bearing green fluorescent protein-tagged polyribosomes (BAC-TRAP mice) provide an exceptional opportunity to identify potential regeneration-associated transcriptional events in a cell-type-specific manner [40].

A book entitled *Animal Models of Acute Neurological Injuries* [42] has provided a wide array of animal models currently used for assessing acute neurological injuries, providing valuable resource for neural regeneration research.

2.2 Labeling and Imaging Technology

How to exquisitely label nerve fibers within the nerve system and their connections to their target continues to be an important concern for neural regeneration research. Transgenic animals that express fluorescent proteins in specific neuronal subsets provide potentially useful tools for the regeneration study of these neurons [38].

Axonal tract tracing technologies are also powerful tools for identifying axonal connections. With appropriate injury models and tracing techniques, the status of axons—sparing, die-back, sprouting, regeneration, or synaptogenesis—can be readily identified [43]. Based on axonal transport, a long series of tracers has been developed as anterograde tracing or retrograde tracing according to the preferential direction of their transport in the axon.

Viruses have been developed for tract-tracing studies. Compared to conventional tracers, viruses have the ability to traverse multisynaptic pathways and replicate to amplify signals at each step in the process [44]. Depending on the species and strain of the virus, viruses can travel preferentially in the anterograde or the retrograde direction or both [45,46]. For example, Wang et al. found that a recombinant adenovirus carrying a green fluorescent protein reporter gene (Adv-GFP) can preferentially, intensely, and bidirectionally label the rat rubrospinal