Chemokine Receptors and NeuroAIDS
Chemokine Receptors and NeuroAIDS
Beyond Co-Receptor Function and Links to Other Neuropathologies

Springer
This book is dedicated in memory of my father, Dante Meucci, a surgeon of rare professional and human qualities who infused my three brothers and me with the passion for science, medicine, and caring for others; and to my mother, Rosaria Rago Meucci for showing me the joy of discoveries and always supporting my choices.
Preface

This is a remarkably timely volume for several distinct reasons. First, it captures an inflection point in the neurological consequences of the HIV pandemic. With the widespread use of highly active anti-retroviral therapy (HAART), devastating syndromes of HIV-associated dementia and vacuolar myelopathy have given way, respectively, to milder complications including cognitive impairment and painful peripheral neuropathy. The present book addresses mechanisms of these contemporary disorders. Second, there is an extensive discussion of pathways by which HIV infection, or its treatment, can lead to pain. Chemokines and their receptors constitute an integral part of this process, and this book contains the largest compilation to date, of concentrated information about the implication of chemokine biology in pain. Lastly, the book addresses chemokine receptor CXCR4 from multiple perspectives. This receptor and CXCL12, its ligand, participate in virtually every phase of biology from development, through organization and deployment of immune and nervous-system elements, infection, immunity, neurophysiology, adult neurogenesis, and functions of numerous tissue stem cells. The combination of these varied unique emphases renders this book highly topical.

Beginning Sect. I, Kolson and colleagues provide a measured consideration of a wide variety of research methods from magnetic resonance spectroscopy (MRS) to analysis of HIV proteins in in vitro systems. Fischer-Smith and Rappaport treat several overlapping topics, in effect yielding a “second opinion” about how to apply current research methods in the study of HIV-related neurological disease. Tan, Hoke, and Nath effectively and forcefully integrate clinical and pathogenetic data related to the crucial topic of HIV disease and peripheral neuropathy. Wigdahl’s group contributes an authoritative and accessible treatment of HIV-viral latency embellished with well-designed graphics to illustrate complex concepts. Klein and coworkers combine a lucid review of chemokine receptors responsible for leukocyte trafficking with the presentation of a novel hypothesis, drawn from their research, about the role of CXCL12/CXCR4 as organizers of CNS perivascular infiltrates.

Section II opens with a fascinating discussion by Vergote, Overall, and Power on how proteolytic cleavage of CXCL12 by MMP2 mediates neurotoxicity via an aberrant ligand–receptor interaction with CXCR3. Rostene et al. provide a succinct summary of the role(s) of CXCR4 in activating nociceptors in the context of HIV
infection plus anti-retroviral agent treatment and also discuss the function(s) of CCL2/CCR2 in generating neuropathic pain. This latter topic is amplified in Miller’s masterful discussion of CCR2 in neuropathic pain, in a chapter which also explains the roles of chemokine receptors in neural development and adult neurogenesis. Khan addresses the complex field of chemokine receptor interactions with cell-cycle regulatory components such as Rb and p53, as an entrée to comparing signaling to CXCR4 by HIV gp120 and the cardinal ligand CXCL12. Rubin contributes a subtle and comprehensive chapter on chemokine receptors in glioma, extending from cell biology to signaling to therapeutic application. Bezzi et al. discuss the critical issue of glutamate as a gliotransmitter, and places CXCR4 in the context of astrocyte regulation of synaptic activity. They incorporate unexpected roles of TNFα and prostaglandins as signaling intermediates, and also cover fully the topic of glutamate exocytosis by astrocytes, and its dysregulation during neuroinflammatory pathologies including HIV-associated cognitive impairment. Limatola and colleagues elegantly dissect how stimulation of CX3CR1 on microglia leads to adenosine production, which acts through A1R adenosine receptor on neurons, mediating neuroprotection.

Section III provides a very extensive and multifaceted treatment of the interactions between the chemokine and opioid system. These interactions affect the roles of chemokine receptors in pain, in HIV infections and immune-system functions, as well as in the emerging role of selected chemokines as neuromodulators/neurotransmitters – aspects that become particularly important when considering the prominent population of HIV-positive individuals who also abuse opiates. A contribution by Roger’s group opens the section; these authors focus on their pioneering work regarding bidirectional communication between chemokine and opioid receptors in immune cells and address the relevance of these interactions to HIV infection. Martin and Roy discuss the major mechanisms of dysregulation of innate immunity by morphine and its implications for HIV progression, while providing interesting insights into the role of these mechanisms in wound healing. Next is a comprehensive review by Hauser et al. about the unique regulation of glial cells by opiates and a detailed dissection of the respective contribution of astroglia and microglia to HIV neuropathology in patients with history of drug abuse. This section is concluded by the work of Sengupta and Meucci introducing novel mechanisms implicated in negative modulation of neuronal CXCR4 by opiates, which significantly alter CXCR4-mediated signaling in the brain. This pathway may have significant consequences for the physiological actions of the CXCR4 receptor in the nervous system and may also promote disease progression.

These contributions represent major groups in this important field and fulfill a notable void in the current literature.

Ohio, USA

Richard M. Ransohoff
Acknowledgments

First, I would like to thank all those who contributed to this book as they enthusiastically agreed to participate in spite of their demanding academic and/or clinical responsibilities. Without their help and friendship, this book would not exist. I feel fortunate to have them as colleagues. In particular, I would like to thank Richard Ransohoff, who provided invaluable insights when the project started, helped me put things in perspective, and kindly wrote the book overview. I also received tremendous and continuous support from Richard J. Miller; while I was in his lab at the University of Chicago, my interest for chemokines sparkled and he let me develop it without any limitation and help me gain independence. I have been lucky to find such great mentors, colleagues, and friends in Philadelphia as well. Some of them, Dennis Kolson, Jay Rappaport, and Brian Wigdahl, also contributed to the book with their own work, and I am grateful for their time and efforts.

My gratitude also goes out to Ann Avouris, Neuroscience Editor at Springer, for guiding me with patience and knowledge through my first book experience. Ann and her assistants, Elisabeth Thompson and Melissa Higgs, made my job easier and more pleasant. It was a new challenge for me, but they made it fun.

I would not be here without the support of the NIH, NIDA in particular, which has generously sponsored my work throughout these years. I am particularly grateful to Charles Sharp, who successfully walked me through my very first grant application as a “new investigator” in 2001. Though he recently retired, he is still very involved with science and always provides precious inputs. Likewise, all the other members of NIDA I have personally interacted with – Diane Lawrence, Albert Avila, David Shurtleff – are always available, supportive, and enthusiastic. Their positive attitude is contagious and helps science move forward.

Special thanks also go out to all the members of my research group that supported this project as needed and nicely coped with my limited availability to them when dealing with any book-related issues. By now they should have returned to be my main priority, so I hope we have fully resumed our regular lab meetings and one-on-one discussions.

Last but not least, I wish to thank my husband and son: they cherish me and make me laugh, and expect nothing but the same in return.

Thank You All

Philadelphia, USA

Olimpia Meucci
Contents

1 Introduction ................................................................. 1

Section I

2 HIV Neuroinvasion: Early Events, Late Manifestations .......... 5
   Maria F. Chen, Samantha Soldan, and Dennis L. Kolson

3 HIV Co-receptors: The Brain Perspective ........................ 33
   Tracy Fischer-Smith and Jay Rappaport

4 HIV Infection and the PNS ............................................. 51
   Kevin Tan, Avindra Nath, and Ahmet Hoke

5 HIV Latency and Reactivation: Role in Neuropathogenesis ...... 87
   Anupam Banerjee, Michael R. Nonnemacher, and Brian Wigdahl

6 HIV Coreceptors and Their Roles in Leukocyte
   Trafficking During Neuroinflammatory Diseases ................. 119
   Robyn S. Klein and Erin E. McCandless

Section II

7 Chemokine Proteolytic Processing in HIV Infection:
   Neurotoxic and Neuroimmune Consequences ..................... 149
   David Vergote, Christopher M. Overall, and Christopher Power

8 Chemokines and Chemokine Receptors in the Brain ............... 173
   Stéphane Mélik Parsadaniantz, Ghazal Banisadr, Philippe Sarret,
   and William Rostène
9 Chemokine Signaling in the Nervous System and Its Role in Development and Neuropathology ......................... 191
Richard J. Miller

10 Modulation of Neuronal Cell Cycle Proteins by Chemokine Receptors and Its Role in the Survival of Postmitotic Neurons .......... 221
Muhammad Z. Khan

11 Chemokines and Primary Brain Tumors .............................................................................. 253
Shyam S. Rao, Mahil Rao, Nicole Warrington, and Joshua B. Rubin

12 Chemokines as Neuromodulators: Regulation of Glutamatergic Transmission by CXCR4-Mediated Glutamate Release From Astrocytes ......................................................................................................................... 271
Corrado Calì, Julie Marchaland, Osvaldo Mirante, and Paola Bezzi

13 Role of CX3CL1 in Synaptic Activity and Neuroprotection ................... 301
Davide Ragozzino, Clotilde Lauro, and Cristina Limatola

Section III

14 Interaction Between Opioid and Chemokine Receptors in Immune Cells: Implications for HIV Infection ................................ 319
Christine Happel, Changcheng Song, Mathew J. Finley, and Thomas J. Rogers

15 Chronic Morphine’s Role on Innate Immunity, Bacterial Susceptibility and Implications in Wound Healing ......................... 337
Josephine Martin and Sabita Roy

16 Opioids, Astroglial Chemokines, Microglial Reactivity, and Neuronal Injury in HIV-1 Encephalitis ........................................ 353
Kurt F. Hauser, Nazira El-Hage, Annadora J. Bruce-Keller, and Pamela E. Knapp

17 Regulation of Neuronal Chemokine Receptor CXCR4 by μ-Opioid Agonists and Its Involvement in NeuroAIDS .............. 379
Rajarshi Sengupta and Olimpia Meucci

About the Editor .................................................................................................................... 399

About the Book ................................................................................................................... 401

Index ..................................................................................................................................... 403
Contributors

**Anupam Banerjee**  
Department of Microbiology and Immunology, Drexel University,  
2900 Queen Lane, Philadelphia, PA, USA

**Paola Bezzi**  
Department of Cellular Biology and Morphology (DBCM), Faculty of Medicine,  
University of Lausanne, UNIL – Bugnon, Rue du Bugnon 21, CH-1015  
Lausanne, Switzerland

**Annadora J. Bruce-Keller**  
Division of Basic Research, Pennington Biomedical Research Center,  
Louisiana State University Baton Rouge, LA, USA

**Maria F. Chen**  
Department of Neurology, Hospital of the University of Pennsylvania,  
3 West Gates, 3400 Spruce Street, Philadelphia, PA, USA

**Cali Corrado**  
Department of Cellular Biology and Morphology (DBCM), Faculty of Medicine,  
University of Lausanne, UNIL – Bugnon, Rue du Bugnon 21, CH-1015  
Lausanne, Switzerland

**Nazira El-Hage**  
Department of Pharmacology & Toxicology, Virginia Commonwealth University,  
School of Medicine, 1217 East Marshall Street, Richmond, VA, USA

**Mathew J. Finley**  
Fels Institute for Cancer Research and Molecular Biology, Temple University  
School of Medicine, 3307 N. Broad Street, Philadelphia, PA, USA

**Tracy Fischer-Smith**  
Department of Neuroscience, Center for Neurovirology, Temple University  
School of Medicine, Philadelphia, PA, USA
Christine Happel  
Fels Institute for Cancer Research and Molecular Biology, Temple University  
School of Medicine, 3307 N. Broad Street, Philadelphia, PA, USA

Kurt F. Hauser  
Department of Pharmacology and Toxicology, Virginia Commonwealth University School of Medicine, 1217 East Marshall Street, Richmond, VA, USA

Ahmet Hoke  
Neuromuscular Division, Department of Neurology, Johns Hopkins University,  
Path 509, 600 N. Wolfe St., Baltimore, MD, USA

Muhammad Z. Khan  
Department of Pharmacology and Physiology, Drexel University College of Medicine, 245 North 15th Street, Philadelphia, PA, USA

Robyn S. Klein  
Department of Internal Medicine, Division of Infectious Diseases, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

Pamela E. Knapp  
Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, 1217 East Marshall Street, Richmond, VA, USA

Dennis L. Kolson  
Department of Neurology, Hospital of the University of Pennsylvania,  
3 West Gates, 3400 Spruce Street, Philadelphia, PA, USA

Clotilde Lauro  
Department of Physiology and Pharmacology, University Sapienza,  
Piazzale A. Moro, 5, 00185 Rome, Italy

Cristina Limatola  
Department of Physiology and Pharmacology, University Sapienza,  
Piazzale A. Moro, 5, 00185 Rome, Italy

Julie Marchaland  
Department of Cellular Biology and Morphology (DBCM), Faculty of Medicine, University of Lausanne, UNIL – Bugnon, Rue du Bugnon 21, CH-1015 Lausanne, Switzerland

Josephine Martin  
Department of Pharmacology, University of Minnesota, 6-120 Jackson Hall,  
312 Church Street SE, Minneapolis, MN, USA

Erin E. McCandless  
Department of Pathology and Immunology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

Olimpia Meucci  
Department of Pharmacology and Physiology & Microbiology and Immunology, Drexel University College of Medicine, New College Building, 8804, 245 N 15th St., Philadelphia, PA, USA
Richard J. Miller
Department of Molecular Pharmacology and Biological Chemistry, Northwestern University School of Medicine, 303 E Chicago Avenue, Chicago, IL, USA

Osvaldo Mirante
Department of Cellular Biology and Morphology (DBCM), Faculty of Medicine, University of Lausanne, UNIL – Bugnon, Rue du Bugnon 21, CH-1015 Lausanne, Switzerland

Avindra Nath
The Johns Hopkins University, 600 N. Wolfe St., Room: 509 Pathology, 600 N. Wolfe St., Baltimore, MD, USA

Michael R. Nonnemacher
Department of Microbiology and Immunology, Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA, USA

Christopher M. Overall
Department of Biochemistry & Molecular Biology, Center for Blood Research, University of British Columbia, 4th Floor, Life Sciences Centre, 2350 Health Sciences Mall, Vancouver, BC, Canada

Stéphane Mélik Parsadaniantz
INSERM U 732-UPMC, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France

Christopher Power
Department of Medicine (Neurology), 6-11 Heritage Medical Research Centre, University of Alberta, Edmonton, AB, Canada T6G 2S2

Davide Ragozzino
Istituto Fisiologia Umana, Piazzale A. Moro 5, I00185 Roma, Italy

Richard M. Ransohoff
Neuroinflammatory Research Center, Lerner Research Institute/NC30, 9500 Euclid Avenue, Cleveland, OH, USA

Mahil Rao
Department of Pediatrics, St. Louis Children’s Hospital, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

Shyam S. Rao
Department of Radiation Oncology, Department of Pediatrics, St. Louis Children’s Hospital, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

Jay Rappaport
Department of Neuroscience, Temple University School of Medicine, 1900 N. 12th St., Biology Life Science Bldg., Rm. 246, Philadelphia, PA, USA
Thomas J. Rogers
Fels Institute for Cancer Research and Molecular Biology, Temple University
School of Medicine, 3307 N. Broad Street, Philadelphia, PA, USA

William Rostène
INSERM U732-UPMC, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France

Sabita Roy
Department of Pharmacology, University of Minnesota, 6-120 Jackson Hall, 312 Church Street SE, Minneapolis, MN, USA

Joshua B. Rubin
Department of Pediatrics, St. Louis Children’s Hospital, Washington University
School of Medicine, Campus Box 8208, 660 South Euclid Avenue, St. Louis, MO, USA

Philippe Sarret
Département de Physiologie et Biophysique, Faculté de Médecine et des Sciences de la Sante, Université de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, QC, Canada

Rajarshi Sengupta
Department of Pharmacology and Physiology, Drexel University
College of Medicine, 245 N 15th St., Philadelphia, PA, USA

Samantha Soldan
Department of Neurology, Hospital of the University of Pennsylvania, 3 West Gates, 3400 Spruce Street, Philadelphia, PA, USA

Changcheng Song
Fels Institute for Cancer Research and Molecular Biology, Temple University
School of Medicine, 3307 N. Broad Street, Philadelphia, PA, USA

Kevin Tan
Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore, Republic of Singapore

David Vergote
Department of Medicine, 6-11 Heritage Medical Research Centre, University of Alberta, Edmonton, AB, Canada T6G 2S2

Nicole Warrington
Department of Pediatrics, St. Louis Children’s Hospital, Washington University
School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

Brian Wigdahl
Department of Microbiology & Immunology (G44), Drexel University, 2900 Queen Lane, Philadelphia, PA, USA
Chapter 1
Introduction

During the last two decades chemokine receptors have consistently been in the spotlight albeit for different reasons. They have “evolved” from coordinators of inflammatory/immune responses to HIV co-receptors, mediators of organogenesis and development, cancer metastases inducers, and neuromodulators. However, it seems that our knowledge of the physiological and pathological roles of this large subfamily of G-protein-coupled receptors has not yet reached a plateau. Novel and essential biological functions of chemokine receptors are continuously being discovered and each of these new discoveries has led to alternative therapeutic strategies that show promise in the treatment of several pathologies, including AIDS and AIDS-related conditions.

HIV neuropathology is a complex disease, whose development and progression depends on the interplay of an array of host and viral factors. Although much has been learned about how the HIV virus may enter and damage the nervous system, the events ultimately leading to neurological dysfunction are still not clear and many questions remain about the factors that affect disease progression. Modern antiretroviral therapies have significantly changed the manifestations of the HIV-induced neurological syndrome, however they have also introduced novel problems, such as ambiguity about the nature of the minor motor cognitive disorders, alteration of the natural disease process (a confounding factor with respect to neuropathogenesis), and, importantly, drug toxicity. Furthermore, owing to their relatively low efficacy to crossing the blood–brain barrier and the presence of viral reservoirs, these drugs still do not provide full protection from HIV entry and replication in the brain. Unfortunately, even though combinatorial antiretroviral therapies have reduced the incidence and severity of the HIV neurological complications, their prevalence has increased due to the longer life span of treated patients.

Excellent publications have previously covered these and other important aspects of HIV neuropathogenesis (see for example “The neurology of AIDS,” 2005 – Oxford University Press), which are not reviewed in the present book. Our focus has been on unresolved or emerging issues concerning the role of chemokine receptors in neuronal injury and HIV neuropathology – including their ability to regulate fundamental neuronal and glial functions, and their role in neurovirulence and neurotoxicity. Although the importance of these molecules in the CNS is now apparent,