Heat Shock Proteins and the Brain: Implications for Neurodegenerative Diseases and Neuroprotection
HEAT SHOCK PROTEINS

Volume 3

Series Editors:

A. A. A. Asea
Effie and Wofford Cain Centennial Endowed Chair in Clinical Pathology,
Chief, Division of Investigative Pathology, Scott & White Memorial Hospital and Clinic
and The Texas A&M Health Science Center, College of Medicine

S. K. Calderwood
Division of Molecular and Cellular Radiation Oncology,
Beth Israel Deaconess Medical Center and Harvard Medical School
Heat Shock Proteins and the Brain: Implications for Neurodegenerative Diseases and Neuroprotection

Edited by

Alexzander A. A. Asea
Effie and Wofford Cain Centennial Endowed Chair in Clinical Pathology, Chief, Division of Investigative Pathology, Scott & White Memorial Hospital and Clinic and The Texas A&M Health Science Center, College of Medicine, Temple, TX, U.S.A.

and

Ian R. Brown
Director, Center for the Neurobiology of Stress, Department of Biological Sciences, University of Toronto at Scarborough, Toronto, ON, Canada
This book is dedicated to our children Colleen, Kitty and Heather (I.R.B.), Alexzander Jr., Vanessa and Edwina (A.A.A.)
TABLE OF CONTENTS

Preface xi
List of Contributors xiii

PART I Heat Shock Proteins and Neurodegenerative Diseases

1. Chaperones and Polyglutamine Expansion Disorders 3
   Martin L. Duennwald

2. Heat Shock Proteins, Unfolded Protein Response Chaperones and Alzheimer’s Disease 25
   Jordi Magrané and Henry W. Querfurth

3. Cellular and Molecular Mechanisms Underlying Parkinson’s Disease: The Role of Molecular Chaperones 51
   Pamela J. McLean

4. Heat Shock Proteins as Therapeutic Targets in Amyotrophic Lateral Sclerosis 69
   Bernadett Kalmar and Linda Greensmith

5. The Role of Chaperones and Co-Chaperones in Retinal Degenerative Diseases 109
   Maria Kosmaoglou, Tatiana V. Novoselova and Michael E. Cheetham

6. Neuroprotective Features of Hsp90 Inhibitors Exhibiting Anti-Inflammatory Actions: Implications for Multiple Sclerosis 125
   Douglas L. Feinstein, Alessandra Spagnolo and Cinzia Dello Russo

7. Role of HspB1 and HspB8 in Hereditary Peripheral Neuropathies: Beyond the Chaperone Function 139
   Serena Carra and Jacques Landry
# Table of Contents

## PART II  Heat Shock Proteins and Neuroprotection

8. Heat Shock Proteins Hsp70 and Hsp27 and Neural Cellular Protection  
   Tracy S. Voegeli, Amanda J. Wintink and R. William Currie  
   [159](#)  

9. Molecular Chaperones and Protection in Animal and Cellular Models of Ischemic Stroke  
   Yi-Bing Ouyang, Lijun Xu and Rona G. Giffard  
   [179](#)  

10. Strategies for Conferring Neuroprotection and Countering the High Threshold for Induction of the Stress Response in Motor Neurons  
    Heather D. Durham  
    [203](#)  

11. Use of Viral Gene Delivery Systems to Investigate the Neuroprotective Roles of Hsp70 and Hsp40 Proteins  
    Joanna Howarth, Do-Young Lee and James B. Uney  
    [223](#)  

    Ian R. Brown  
    [239](#)  

## PART III  Extracellular Heat Shock Proteins and the Nervous System

    Michael Tytell, Mac B. Robinson and Carolanne E. Milligan  
    [257](#)  

14. Silencing of Metastasis-Associated Gene 1 (MTA1) Stimulates Hsp70 Cellular Release and Neurite Extension in Neuroblastoma Cells  
    Nirmal K. Singh, Preethi Rao and Alexzander Asea  
    [273](#)  

15. Extracellular Chaperones and Amyloids  
    Mark R. Wilson, Justin J. Yerbury and Stephen Poon  
    [283](#)  

## PART IV  Aging, Control of Life Span and Expression of Heat Shock Proteins

    Robert M. Tanguay and Geneviève Morrow  
    [319](#)  

17. Mechanistic Links Between Aging and Aggregation-Mediated Proteotoxicity: Role of HSF-1 and DAF-16  
    Ehud Cohen and Andrew Dillin  
    [337](#)
Table of Contents

18. Protein Quality Control and Heat Shock Gene Expression in the Nervous System 349
   Stuart K. Calderwood

19. Serum Hsp70 Level as a Biomarker of Exceptional Longevity 365
   Dellara F. Terry and Alexzander Asea

Index 371
PREFACE

With the prevalence of neurodegenerative diseases on the rise as average life expectancy increases, the hunt for effective treatments and preventive measures for these disorders is a pressing challenge. Neurodegenerative disorders such as Alzheimer’s disease, Huntington’s disease, Parkinson’s disease and amyotrophic lateral sclerosis have been termed ‘protein misfolding disorders’ that are characterized by the neural accumulation of protein aggregates. Manipulation of the cellular stress response involving the induction of heat shock proteins offers a therapeutic strategy to counter conformational changes in neural proteins that trigger pathogenic cascades resulting in neurodegenerative diseases. Heat shock proteins are protein repair agents that provide a line of defense against misfolded, aggregation-prone proteins.

Heat Shock Proteins and the Brain: Implications for Neurodegenerative Diseases and Neuroprotection reviews current progress on neural heat shock proteins (HSP) in relation to neurodegenerative diseases (Part I), neuroprotection (Part II), extracellular HSP (Part III) and aging and control of life span (Part IV). Key basic and clinical research laboratories from major universities and hospitals around the world contribute chapters that review present research activity and importantly project the field into the future. The book is a must read for researchers, postdoctoral fellows and graduate students in the fields of Neuroscience, Neurodegenerative Diseases, Molecular Medicine, Aging, Physiology, Pharmacology and Pathology.

Alexzander A. A. Asea and Ian R. Brown
LIST OF CONTRIBUTORS

Alexzander Asea
Division of Investigative Pathology, Scott and White Memorial Hospital and Clinic and The Texas A&M Health Science Center, College of Medicine, Temple, TX, USA

Ian R. Brown
Center for the Neurobiology of Stress, Department of Biological Sciences, University of Toronto at Scarborough, Toronto, ON, Canada

Stuart K. Calderwood
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Serena Carra
Department of Radiation and Stress Cell Biology, University Medical Center Groningen, Groningen, The Netherlands

Michael E. Cheetham
Division of Molecular and Cellular Neuroscience, Institute of Ophthalmology, University College London, London, UK

Ehud Cohen
Molecular and Cell Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, USA

R. William Currie
Department of Anatomy and Neurobiology, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada

Cinzia Dello-Russo
Department of Pharmacology, Catholic University Medical School, Rome, Italy

Andrew Dillin
Molecular and Cell Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, USA

Martin L. Duennwald
Boston Biomedical Research Institute, Watertown, MA, USA
Heather D. Durham
Department of Neurology/Neurosurgery and Montreal Neurological Institute,
McGill University, Montreal, QC, Canada

Douglas L. Feinstein
Department of Anesthesiology, University of Illinois, and Jesse Brown Veteran’s Affairs Research Division, Chicago, IL, USA

Rona G. Giffard
Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, USA

Linda Greensmith
Institute of Neurology, University College London, Queen Square, London, UK

Joanna Howarth
Neuroregenerative Medicine Group, Laboratories for Integrated Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Bernadett Kalmar
Institute of Neurology, University College London, Queen Square, London, UK

Maria Kosmaoglou
Division of Molecular and Cellular Neuroscience, Institute of Ophthalmology,
University College London, London, UK

Jacques Landry
Centre de recherche en cancérologie de l’Université Laval, L’Hôtel-Dieu de Québec, Québec, QC, Canada

Do-Young Lee
Neuroregenerative Medicine Group, Laboratories for Integrated Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Jordi Magrané
Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, USA

Pamela J. McLean
Mass General Institute for Neurodegenerative Disease (MIND), Massachusetts General Hospital, Charlestown, MA, USA

Caroline E. Milligan
Department of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, NC, USA
List of Contributors

Geneviève Morrow
Lab of Cellular and Developmental Genetics, Department of Medicine, Université Laval, Québec, QC, Canada

Tatiana V. Novoselova
Division of Molecular and Cellular Neuroscience, Institute of Ophthalmology, University College London, London, UK

Yi-Bing Ouyang
Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, USA

Stephen Poon
School of Biological Sciences, University of Wollongong, Wollongong, NSW, Australia

Henry W. Querfurth
Department of Neurology, Caritas St Elizabeth’s Medical Center, Tufts University School of Medicine, Boston, MA, USA

Preethi Rao
Division of Investigative Pathology, Scott and White Memorial Hospital and Clinic Temple, TX, USA

Mac B. Robinson
Department of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Nirmal K. Singh
Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Alessandra Spagnolo
Department of Anesthesiology, University of Illinois, and Jesse Brown Veteran’s Affairs Research Division, Chicago, IL, USA

Robert M. Tanguay
Lab of Cellular and Developmental Genetics, Department of Medicine, Université Laval, Québec, QC, Canada

Dellara F. Terry
Geriatrics Section, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

Michael Tytell
Department of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, NC, USA
List of Contributors

James B. Uney
Neuroregenerative Medicine Group, Laboratories for Integrated Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Tracy S. Voegeli
Department of Anatomy and Neurobiology, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada

Mark R. Wilson
School of Biological Sciences, University of Wollongong, Wollongong, NSW, Australia

Amanda J. Wintink
Department of Pharmacology, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada

Lijun Xu
Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, USA

Justin J. Yerbury
School of Biological Sciences, University of Wollongong, Wollongong, NSW, Australia
PART I

HEAT SHOCK PROTEINS
AND NEURODEGENERATIVE DISEASES