PROTEIN FOLDING AND MISFOLDING: NEURODEGENERATIVE DISEASES

FOCUS ON STRUCTURAL BIOLOGY

Volume 7

Series Editor

ROB KAPTEIN

Bijvoet Center for Biomolecular Research,
Utrecht University, The Netherlands

Protein Folding and Misfolding: Neurodegenerative Diseases

Edited by

JUDIT OVÁDI

Hungarian Academy of Sciences, Biological Research Center, Institute of Enzymology, Hungary

and

FERENC OROSZ

Hungarian Academy of Sciences, Biological Research Center, Institute of Enzymology, Hungary

Springer

Editors
Judit Ovádi
Hungarian Academy of Sciences
Biological Research Center
Institute of Enzymology
Karolina út 29
Budapest 1113
Hungary
ovadi@enzim.hu

Ferenc Orosz
Hungarian Academy of Sciences
Biological Research Center
Institute of Enzymology
Karolina út 29
Budapest 1113
Hungary
orosz@enzim.hu

ISBN: 978-1-4020-9433-0 e-ISBN: 978-1-4020-9434-7

DOI 10.1007/978-1-4020-9434-7

Library of Congress Control Number: 2008938904

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

springer.com

Foreword

It was twenty five years ago this year that for the first time a protein underlying a form of human cerebral amyloidosis, the Icelandic-type hereditary cerebral haemorrhage was identified. This, together with the recognition that an amino acid substitution can transform the wild type cystatin C into a disease-associated amyloid-forming protein in this condition, was only a prelude to a series of important discoveries that followed. As a result, pathologically altered proteins have been brought into the centre stage of research into the pathomechanism of a number of neurodegenerative diseases, which include epidemiologically such important conditions as Alzheimer's disease or Parkinson's disease and, among others, also the transmissible spongiform encephalopathies, Huntington's chorea, spinocerebellar ataxias, frontotemporal lobar degenerations and amyotrophic lateral sclerosis. Despite the diversity in the amino acid sequence of the different proteins involved in these neurological diseases, one of the common themes underlying the pathomechanisms of all these conditions is protein misfolding, aggregation – hence the term protein folding disorders –, which can trigger cascades of events ultimately resulting in synapse loss and neuron death with devastating clinical consequences in many of the most precious spheres of human existence including personality, cognition, memory, skilled movements and affection.

It is always a challenging task to unite the different topics of the individual chapters into a common theme in a multi-author volume, but the current book edited by Judit Ovadi and Ferenc Orosz fits this task admirably. The contributors of the chapters are very well-chosen to cover a good number of topical areas of neurodegenerative research. Without exception the chapters set forth clearly the current understanding of their chosen topics, which will allow both the specialist reader and the novice entering into the field to acquire the information they require to find. I have no hesitation in expecting that this wisely edited book will shortly become a well-thumbed text on the bookshelves of many research libraries and offices.

London July 2008

Tamas Revesz FRCPath
Professor of Neuropathology
Institute of Neurology
University College London
UK

Preface

The worldwide ageing of populations has brought the neurodegenerative diseases into the focus of interest. These diseases constitute large variety of pathological conditions originating from the slow, irreversible and systemic loss of cells in different regions of the brain resulting in degenerative problems with distinct clinical symptoms. The pathological behaviors are frequently associated with "proteinopathies", the non-physiological behavior of a specific protein, affecting its processing, functioning, and/or folding. These proteins do not have stable tertiary and/or secondary structures in vivo; they enter into aberrant interactions affecting their folding state and function. A number of the diverse human neurodegenerative diseases are now recognized as conformational diseases because these are caused by aggregations of unfolded or misfolded proteins. Knowledge on the intrinsically unstructured proteins, a relatively newly recognized family of gene products as well as on the misfolded proteins produced by genetic mutations or environmental effects has been extensively accumulated in the past years. These proteins frequently cause proteolytic stress and/or enter into aberrant, non-physiological protein–protein interactions leading to sequestration of protein aggregates which are assemblies of many not-yet-identified components in addition to the deposition of well-characterized misfolded peptides and proteins. Such fate is known in the cases of Aβ peptide and tau protein in Alzheimer's disease, α-synuclein in Parkinson's disease, the extended polyglutamine stretch of mutant huntingtin in Huntington's disease and the prion protein in prion diseases. These protein assemblies display diverse ultrastructures such aggresomes, fibers, oligomers or amorphous structures, however, the nature of these species concerning their cytoprotective or cytotoxic effects has not been clarified yet. The understanding of the course and pathomechanism of the diseases arising from interactions of the so called malfolded proteins is crucial for finding effective therapeutic interventions. The identification of aberrant protein-protein interaction(s) playing constitutive role in aggregate formation contributes to the development of new pharmacofors that could prevent or circumvent the development of neurodegenerative disorders in human.

The main focus of this issue is to review the molecular events initiated by unfolded or misfolded proteins leading to cell death via the development of pathological inclusions, with special emphasis on the macromolecular associations of the

malfolded proteins into characteristic ultrastructures found in the cases of neurological disorders, some of them are shown in this issue. There are papers which uncover in details the intriguing interconnections between intrinsic disorder and human neurodegenerative diseases; the characterization of the diseases in relation to their hallmark proteins and ultrastructures. Other papers provide conceptual background of the molecular mechanism of the tendency of disordered proteins for aggregation in vitro and in vivo connected with misfolding diseases. Due to the fundamental biological importance of protein aggregates, and our poor knowledge about the molecular basis or specificity of the general phenomenon of protein aggregation, this problem will be specifically discussed. In the light of the protein based neuropathology the classification of the human neurodegenerative diseases is presented. This book also reviews the structural knowledge accumulated for well-studied and for newly discovered proteins involved in paradigmatic conformational disorders with the aim to broaden our understanding of the pathomechanisms of neurodegeneration, which is crucial for finding effective therapeutic interventions that could prevent or circumvent the development of neurodegenerative disorders in humans.

Acknowledgments We are grateful to the Hungarian National Scientific Research Fund (OTKA) and the European Union FP6-2003-LIFESCIHEALTH-I Biosim Fund for providing many years of valuable support to our research, which has also enabled us to edit this volume.

Budapest
July 2008

Judit Ovádi
Ferenc Orosz
Institute of Enzymology, BRC
Hungarian Academy of Sciences
Budapest, Hungary

Contents

Contributors

Ettore Benedetti Dipartimento delle Scienze Biologiche & C.I.R.Pe.B.,Università degli Studi Federico II di Napoli, Napoli, Italy

Herbert Budka Institute of Neurology, Medical University of Vienna, AKH 4J, POB 48, A-1097 Wien, Austria

Veronika Csizmók Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: csv@enzim.hu

David Eliezer Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA, e-mail: eliezer@med.cornell.edu

Jeroen J.M. Hoozemans Department of Pathology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands, e-mail: jjm.hoozemans@vumc.nl

Haruhisa Inoue Department of Neurology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan, e-mail: haruhisa@kuhp.kyoto-u.ac.jp

Ole Isacson Neuroregeneration Laboratories and Center for Neuroregeneration Research at McLean Hospital/Harvard Medical School, NINDS Morris K. Udall Parkinson's Disease Research Center of Excellence, 115 Mill Street, Belmont, MA 02478, USA, e-mail: isacson@mclean.harvard.edu

Poul Henning Jensen Institute of Medical Biochemistry, University of Aarhus, Ole Worms Allé 1.170, DK-8000 Aarhus C, Denmark, e-mail: phj@biokemi.au.dk

Takayuki Kondo Department of Neurology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Gabor G. Kovacs Institute of Neurology, Medical University of Vienna, AKH 4J, POB 48, A-1097 Wien, Austria, e-mail: gabor.kovacs@meduniwien.ac.at

Christine Lund Kragh Institute of Medical Biochemistry, University of Aarhus, Ole Worms Allé 1.170, DK-8000 Aarhus C, Denmark, e-mail: clp@biokemi.au.dk

Attila Lehotzky Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: lehotzky@enzim.hu

Kah-Leong Lim Neurodegeneration Research Laboratory, National Neuroscience Institute, Singapore and Duke-NUS Graduate Medical School, Singapore; 11 Jalan Tan Tock Seng, 308433, Singapore, e-mail: Kah_Leong_Lim@nni.com.sg

Ling Lin Neuroregeneration Laboratories and Center for Neuroregeneration Research at McLean Hospital/Harvard Medical School, NINDS Morris K. Udall Parkinson's Disease Research Center of Excellence 115 Mill Street, Belmont, MA 02478, USA, e-mail: llin@mclean.harvard.edu

Fang Liu Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907-2091, USA

Sha Mi Department of DiscoveryNeurobiology, Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142, United States, e-mail:sha.mi@biogenidec.com

Judit Oláh Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: olju@enzim.hu

Ferenc Orosz Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: orosz@enzim.hu

Judit Ovádi Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: ovadi@enzim.hu

Pasquale Palladino Dipartimento delle Scienze Biologiche & C.I.R.Pe.B., Università degli Studi Federico II di Napoli, Napoli, Italy

Raffaele Ragone Dipartimento di Biochimica e Biofisica & CRISCEB, Seconda Università di Napoli, Napoli, Italy

Tamas Revesz Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK, e-mail: T.Revesz@ion.ucl.ac.uk

Jean-Christophe Rochet Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907-2091, USA, e-mail: rochet@pharmacy.purdue.edu.

Luisa Ronga Dipartimento delle Scienze Biologiche & C.I.R.Pe.B., Università degli Studi Federico II di Napoli, Napoli, Italy

Filomena Rossi Dipartimento delle Scienze Biologiche-Sez. Biostrutture, Università degli Studi "Federico II" di Napoli, Via Mezzocannone, 16, I-80134 Napoli, Italy, e-mail: filomena.rossi@unina.it

Wiep Scheper Neurogenetics Laboratory and Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Ryosuke Takahashi Department of Neurology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan, e-mail: ryosuket@kuhp.kyoto-u.ac.jp

Jeanne M.M. Tan Neurodegeneration Research Laboratory, National Neuroscience Institute, Singapore, Singapore

Peter Tompa Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Karolina út 29, Budapest, H-1113 Hungary, e-mail: tompa@enzim.hu

Esther S.P. Wong Neurodegeneration Research Lab, National Neuroscience Institute, Singapore and Department of Anatomy and Structural Biology, Marion Bessin Liver Research Center, Albert Einstein College of Medicine, USA

Vladimir N. Uversky Center for Computational Biology and Bioinformatics, Department of Biochemistry and Molecular Biology, Institute for Intrinsically Disordered Protein Research, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA and Institute for Biological Instrumentation, Russian Academy of Sciences 142290 Pushchino, Moscow Region, Russia And Molecular Kinetics, Inc., Indianapolis, IN 46268, USA, e-mail: vuversky@iupui.edu