

Contents

Contributors.....	xi
Preface.....	xiii
 Pathologic Lesions in Neurodegenerative Diseases.	 1
Paul M. Thompson and Harry V. Vinters	
I. Introduction	2
II. Parkinsonian Signs and Symptoms (“Parkinsonism”), PD, and Diffuse Lewy Body Disease	23
III. Frontotemporal Lobar Degeneration(s).....	28
IV. Other (Miscellaneous) Disorders	32
V. Conclusion and Future Directions	33
Acknowledgments	33
References	33
 Cerebral Amyloid Angiopathy	 41
Masahito Yamada and Hironobu Naiki	
I. Introduction	42
II. Clinical Aspects of CAA	42
III. Molecular Aspects of CAA.....	56
IV. Reflections	65
Acknowledgments	67
References	68
 The Genetics of Alzheimer’s Disease.	 79
Lars Bertram and Rudolph E. Tanzi	
I. Introduction	80
II. Early-Onset Familial AD with Mendelian Transmission	84
III. Late-Onset AD Without Mendelian Transmission	87
IV. Outlook for Future Genetics Studies of AD	94
V. Conclusion	95
References	96

Alzheimer's Disease and the Amyloid β -Protein 101

Dominic M. Walsh and David B. Teplow

I. Clinical Features of Alzheimer's Disease.....	101
II. Genetics and Molecular Biology of Alzheimer's Disease.....	102
III. The Amyloid Cascade Hypothesis.....	106
IV. The Amyloid β -Protein—Lessons from <i>In Vitro</i> Studies	107
V. The Amyloid β -Protein—Lessons from the Human Brain	111
VI. Testing the Amyloid Hypothesis in Humans	113
Acknowledgment.....	115
References.....	115

Molecular Insights into Parkinson's Disease. 125

Jean-Christophe Rochet, Bruce A. Hay, and Ming Guo

I. Introduction.....	126
II. Role of α Synuclein Aggregation in PD	127
III. Role of Mitochondrial Dysfunction in PD.....	148
IV. Convergent Pathways and Future Directions.....	160
Acknowledgments	162
References.....	162

Huntington Disease and the Huntingtin Protein 189

Zhiqiang Zheng and Marc I. Diamond

I. Introduction.....	190
II. Genetic and Clinical Features.....	190
III. Structural Features of the Huntingtin Protein.....	192
IV. Htt Function(s).....	193
V. Animal Models of Huntington Disease	195
VI. Pathogenesis of HD.....	197
VII. Therapeutic Targets for HD	201
VIII. Conclusion.....	204
References.....	205

The Complex Molecular Biology of Amyotrophic Lateral Sclerosis (ALS). 215

Rachel L. Redler and Nikolay V. Dokholyan

I. ALS Is a Deadly Neurodegenerative Disorder	216
II. Etiology of ALS	217
III. SOD1-Related Pathology as a General Model for ALS.....	219

IV. Misfolding and Aggregation Is the Most Likely Source of SOD1 Toxicity	219
V. Motor Neuron Death in ALS: Apoptotic Versus Necrotic, Cell-Autonomous Versus Non-Cell-Autonomous	227
VI. ALS Comprises a Spectrum of Pathologies.....	230
VII. Concluding Remarks	241
References.....	242

Tau and Tauopathies. 263

Gloria Lee and Chad J. Leugers

I. Tau Gene and Isoforms.....	264
II. Tau in Neurodegenerative Disease	266
III. Interactions with the Cytoskeleton	268
IV. Phosphorylation and Other Post-translational Modifications.....	272
V. Other Interactions	275
VI. Reflections	279
References	279

Membrane Pores in the Pathogenesis of Neurodegenerative Disease. 295

Bruce L. Kagan

I. Introduction	296
II. Aggregation and the β -Sheet Conformation	297
III. A β	299
IV. Prion Channels.....	303
V. α -Synuclein	305
VI. AG Triplet Repeat Diseases/Huntington's	307
VII. Amyotrophic Lateral Sclerosis/Superoxide Dismutase	308
VIII. How Channels Damage Neurons.....	309
IX. Molecular Pore Models.....	312
X. β -Sheet Conformation and Amyloid Peptide Channels.....	314
XI. Reflections	316
Acknowledgments.....	319
References	320

Protein Quality Control in Neurodegenerative Disease 327

Jason E. Gestwicki and Dan Garza

I. Overview of Protein Quality Control.....	328
---	-----

II. Proteotoxic Proteins and Quality Control	337
III. Reflections and Prospectus.....	342
References.....	346

Biology of Mitochondria in Neurodegenerative Diseases 355

Lee J. Martin

I. Introduction	357
II. Some Aspects of Mitochondrial Biology Relevant to Neurodegeneration	359
III. Mitochondria and Cell Death	363
IV. Mitochondrial Autophagy.....	373
V. Mitochondrial Fission and Fusion.....	374
VI. Mitochondrial Involvement in Adult-Onset Neurodegenerative Diseases.....	374
VII. Reflections	396
Acknowledgments.....	396
References	396

Fungal Prions. 417

Gemma L. Staniforth and Mick F. Tuite

I. Introduction.....	418
II. Establishing the Existence of Prions in Fungi	419
III. The Prions of Yeast and Their Cellular Roles.....	423
IV. Propagating the [<i>PRION</i> ⁺] State	428
V. Yeast Prion Variants and Phenotypic Variability	436
VI. Fungal Prions: Friend or Foe?.....	439
VII. Yeast Prions for Therapeutic Discovery	443
VIII. Reflections	446
Acknowledgments	447
References.....	447
Index.....	457