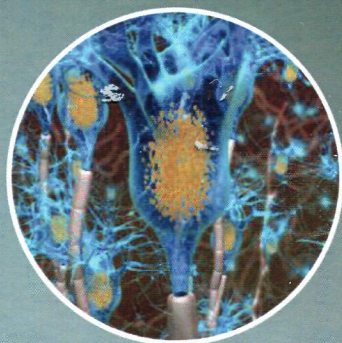
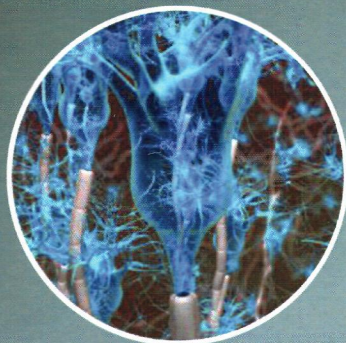
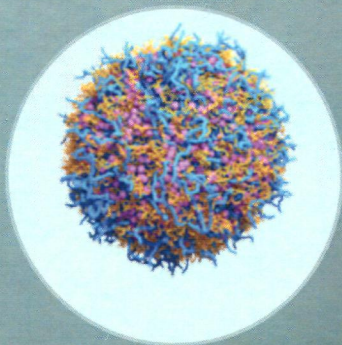


WILEY SERIES IN PROTEIN AND PEPTIDE SCIENCE
Vladimir N. Uversky, Series Editor



PROTEIN OXIDATION AND AGING

Tilman Grune, Betül Catalgol, AND Tobias Jung



PROTEIN OXIDATION AND AGING

**TILMAN GRUNE
BETUL CATALGOL
TOBIAS JUNG**

 **WILEY**

A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2013 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permissions>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Grune, Tilman.

Protein oxidation and aging / by Tilman Grune, Betül Catalgol, Tobias Jung.

p. ; cm. – (Wiley series on protein and peptide science)

Includes bibliographical references and index.

ISBN 978-0-470-87828-6 (cloth : alk. paper)

I. Catalgol, Betül. II. Jung, Tobias (Research associate) III. Title. IV. Series: Wiley series in protein and peptide science.

[DNLM: 1. Proteins–metabolism. 2. Aging–physiology. 3. Neurodegenerative Diseases–etiology. 4. Oxidative Stress–physiology. 5. Proteins–physiology. QU 55]

612.3'98–dc23

2012040264

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTENTS

Introduction to the <i>Wiley Series on Protein and Peptide Science</i>	xi
Preface	xiii
1 Oxidative Stress and Protein Oxidation	1
1.1 The Large Variety of Protein Oxidation Products, 7	
1.1.1 Primary Protein Oxidation Products, 7	
1.1.1.1 Carbon-Centered Radicals, 9	
1.1.1.2 Thiyl Radicals, 13	
1.1.1.3 Aromatic Ring-Derived Radicals, 13	
1.1.1.4 Transfer between Sites, 16	
1.1.2 Reactive Compounds Mediating in Protein Oxidation, 18	
1.1.2.1 Hydroxyl Radical, 20	
1.1.2.2 Superoxide Radicals, 21	
1.1.2.3 Hydrogen Peroxide, 24	
1.1.2.4 Lipid Peroxyl Radicals, 24	
1.1.2.5 Alkoxy Radicals, 24	
1.1.2.6 $\cdot\text{NO}$ and Peroxynitrite, 25	
1.1.2.7 Hypochlorous Acid, 30	
1.1.3 Enzymatic Systems Playing a Role in Protein Oxidation, 31	
1.1.3.1 NADPH Oxidase, 32	
1.1.3.2 Lipoxygenases, 35	
1.1.3.3 Protein Kinases, 35	
1.1.3.4 Mixed-Function Oxidases, 36	
1.1.3.5 Nitric Oxide Synthetase (NOS), 38	

- 1.1.3.6 Myeloperoxidase, 41
- 1.1.3.7 Cyclooxygenase, 42
- 1.1.4 Protein Oxidation in Cells and Cellular Structures, 43
 - 1.1.4.1 Protein Oxidation in Blood and Blood Cells, 43
 - 1.1.4.2 Protein Oxidation of Glycolytic Enzymes and Mitochondria, 46
 - 1.1.4.2.1 Glycolytic Enzymes, 48
 - 1.1.4.2.2 Aconitase, 49
 - 1.1.4.2.3 Carnitine Palmitoyltransferase-1, 49
 - 1.1.4.3 Cytochrome P450 Enzymes, 49
 - 1.1.4.4 Protein Oxidation in the Nucleus and Chromatin, 50
 - 1.1.4.4.1 Histone Modification, 50
 - 1.1.4.5 Protein Oxidation in the Endoplasmic Reticulum, 52
 - 1.1.4.6 Protein Oxidation in Peroxisomes, 54
- 1.2 Reversible Oxidative Modifications, 55
 - 1.2.1 Methionine Sulfoxides and Methionine Modifications, 55
 - 1.2.2 Cysteine Modifications and Disulfide Bond Formation, 61
 - 1.2.3 Surface Hydrophobicity Modifications, 64
- 1.3 Irreversible Oxidation Products, 64
 - 1.3.1 Protein Oxidation and Enzymatic Posttranslational Modifications, 65
 - 1.3.2 Deamidation and Transamination, 66
 - 1.3.3 Protein Glycation and AGEs, 67
 - 1.3.3.1 Receptor for Advanced Glycation End Products (RAGE), 75
 - 1.3.3.2 N^ε-Carboxymethyllysine and N^ε-Carboxyethyllysine, 76
 - 1.3.3.3 Pentosidine, 76
 - 1.3.4 Racemization, 77
 - 1.3.5 Nitrosylation, 77
 - 1.3.6 Tyrosyl Radicals and Nitrotyrosines, 78
 - 1.3.6.1 Dityrosines, 79
 - 1.3.7 Protein Carbonyls, 80
 - 1.3.8 Aldehyde-Protein Reactions, 81
 - 1.3.8.1 MDA-Protein Adducts, 82
 - 1.3.8.2 4-Hydroxy-2,3-Nonenal-Protein Adducts, 82
 - 1.3.9 Cross-Linking of Proteins, 82
- 1.4 The Oxidation of Extracellular Matrix, Membrane and Cytoskeletal Proteins, 83
 - 1.4.1 Collagen, 84
 - 1.4.2 Elastin, 95
 - 1.4.3 The Oxidation of Membrane Proteins, 97

- 1.4.4 Band 3, 97
- 1.4.5 Actin, 99
- 1.5 Mechanism and Factors Influencing the Formation of Protein Oxidation Products, 100
 - 1.5.1 Redox Status, 101
 - 1.5.2 Protein Turnover, 106
 - 1.5.3 Metal-Catalyzed Oxidation (MCO), 107
 - 1.5.4 Heat Shock Proteins, 109
- 1.6 Protein Aggregates: Formation and Specific Metabolic Effects, 111
 - 1.6.1 Accumulation of Oxidized Proteins, 113
 - 1.6.2 Lipofuscin and Ceroid, 115
- 1.7 Methods to Measure Protein Oxidation Products in Research Laboratories, 119
 - 1.7.1 Determination of Methionine Sulfoxide Reduction and Methionine Oxidation, 120
 - 1.7.2 Determination of Protein Glycation and Adducts, 121
 - 1.7.3 Analysis of Isoaspartate Formation, 122
 - 1.7.4 Measurement of Fragmentation, 122
 - 1.7.5 Measurement of Tyrosine Oxidation, 123
 - 1.7.6 Protein Carbonyl Measurement, 124
 - 1.7.7 Radioactive Labeling Protocols for Proteolysis and Aggregation Measurements, 128
 - 1.7.8 Standard Chromatographic Methods for the Measurement of Protein Modifications, 132
 - 1.7.9 Liquid Chromatography Techniques Supported by Mass Spectrometry, 133
 - 1.7.10 GC/MS, 134
 - 1.7.11 Analysis of Protein-Bound 3-Nitrotyrosine by a Competitive ELISA Method, 134
 - 1.7.12 Protein Oxidation Products as Biomarkers in Clinical Science, 135
- References, 139

2 Removal of Oxidized Proteins

215

- 2.1 The Limited Repair of Some Oxidized Proteins, 216
 - 2.1.1 Thiol Repair, 216
 - 2.1.2 Methionine Sulfoxide Reductases, 219
- 2.2 Proteolysis, 221
 - 2.2.1 The Proteasomal System and Its Role in the Degradation of Oxidized Proteins, 222
 - 2.2.1.1 The Ubiquitin-Proteasome System (UPS), 222
 - 2.2.1.2 The Components of the UPS, 222
 - 2.2.1.2.1 The 20S Proteasome, 222
 - 2.2.1.2.2 The Inducible Forms of the Proteasome and Their Function, 227

- 2.2.1.2.3 The 11S Regulator, 231
- 2.2.1.2.4 The 19S Regulator and the UPS, 233
- 2.2.1.2.5 The PA200 Regulator Protein, 238
- 2.2.1.2.6 Cellular Proteasome Inhibitors, 239
- 2.2.1.3 Low-Molecular-Weight Proteasome Inhibitors, 239
- 2.2.1.4 Cellular Function of the UPS, 241
- 2.2.1.5 The Degradation of Oxidized Proteins: A Function of the 20S Proteasome, 243
 - 2.2.1.5.1 Early Studies on the Turnover of Oxidized Proteins, 244
 - 2.2.1.5.2 *In Vitro* Studies and the Recognition of Oxidized Proteins by the Proteasome, 244
 - 2.2.1.5.3 Cellular and *In Vivo* Studies of the Degradation of Oxidized Proteins, 248
 - 2.2.1.5.4 The Inhibition of the Proteasome by Cross-Linked Oxidized Proteins and Proteasomal Regulation during Oxidative Stress, 251
- 2.3 The Role of Other Proteases in the Fate of Oxidized Proteins, 254
 - 2.3.1 Lysosomal Degradation of Oxidized Proteins and the Role of Autophagy, 254
 - 2.3.2 Mitochondrial Degradation of Oxidized Proteins and the Lon Protease, 256
 - 2.3.3 The Uptake of Extracellular Oxidized Proteins and the Role of the Proteasome in Their Degradation, 258
 - 2.3.4 Calpains and the Degradation of Oxidized Proteins, 259
- 2.4 Role of Heat Shock Proteins in Protein Degradation, 260
- 2.5 Conclusion, 262
 - References, 262

3 Protein Oxidation and Aging: Different Model Systems and Affecting Factors

295

- 3.1 Protein Oxidation during Aging: Lower Organisms and Cellular Model Systems, 297
 - 3.1.1 Yeast, 297
 - 3.1.1.1 *Saccharomyces cerevisiae*, 297
 - 3.1.1.2 *Schizosaccharomyces pombe*, 301
 - 3.1.2 *Podospora anserina*, 301
 - 3.1.3 Bacteria, 302
 - 3.1.3.1 *Escherichia coli*, 302
 - 3.1.4 Cell Cultures, 304

- 3.2 Nonmammalian Model Systems and the Accumulation of Oxidized Proteins during Aging, 308
 - 3.2.1 *Caenorhabditis elegans*, 308
 - 3.2.2 *Drosophila melanogaster*, 310
 - 3.2.3 Aquatic Systems, 313
 - 3.2.4 Plants, 315
 - 3.2.5 Amphibians, 317
- 3.3 Age-Related Protein Oxidation in Humans and Mammals, 317
 - 3.3.1 Humans, 317
 - 3.3.2 Animals, 319
 - 3.3.2.1 Rabbits, 323
 - 3.3.2.2 Mice, 324
 - 3.3.2.3 Rats, 327
 - 3.3.2.4 Gerbils, 329
 - 3.3.2.5 Primates, 330
- 3.4 Inherited Factors Influencing Protein Oxidation during Aging, 331
 - 3.4.1 Genetic Instability, Mutations, and Polymorphism, 331
 - 3.4.2 Gender, 333
 - 3.4.3 Vitagenes, 334
 - 3.4.4 Signal Transduction and Transcription Factors, 335
 - 3.4.5 Ion Channels, 340
- 3.5 Age-Related Protein Aggregate Formation in Model Systems, 341
- 3.6 Environmental Factors Affecting Healthy Aging, 342
 - 3.6.1 UV-Induced Skin Photoaging and Skin Aging, 344
 - 3.6.2 Pesticides, 348
 - 3.6.3 Exercise, 349
 - 3.6.4 Dietary Factors and Prevention Strategies, 351
 - 3.6.4.1 Melatonin, 353
 - 3.6.4.2 Growth Hormone, 354
 - 3.6.4.3 Biotrace Metal Elements: Zinc, 356
 - 3.6.4.4 Ascorbic Acid, 357
 - 3.6.4.5 Vitamin E, 360
 - 3.6.4.6 Carnitine and Acetyl-L-Carnitine, 361
 - 3.6.4.7 Homocysteine, 362
 - 3.6.4.8 Ubiquinone, Coenzyme Q₁₀, 363
 - 3.6.4.9 Carnosine, 363
 - 3.6.4.10 Lipoic Acid, 364
 - 3.6.4.11 N-Acetyl-L-Cysteine, 365
 - 3.6.5 Pharmacological Response and Biotransformation in Aging, 365
 - 3.6.5.1 Plant Extracts, 366
 - 3.6.5.2 Polyphenols and Flavonoids, 366
 - 3.6.5.3 Resveratrol, 367
 - 3.6.5.4 AGE and ALE Inhibitors, 368
 - 3.6.6 Caloric Restriction, 369

- 3.7 Repair and Degradation of Oxidized Proteins during Aging, 370
References, 372

4 Protein Oxidation in Some Age-Related Diseases 417

- 4.1 Protein Oxidation during Neurodegeneration and Neurological Diseases, 417
- 4.1.1 Brain Aging, 418
 - 4.1.2 Alzheimer's Disease, 420
 - 4.1.3 Parkinson's Disease, 424
 - 4.1.4 Huntington's Disease, 425
 - 4.1.5 Stroke, 427
 - 4.1.6 Amyotrophic Lateral Sclerosis, 427
- 4.2 Protein Oxidation in Cardiac Diseases, 429
- 4.2.1 Ischemia-Reperfusion, 429
 - 4.2.2 Atherosclerosis, 430
- 4.3 Protein Oxidation in Diabetes, 431
- 4.4 Protein Oxidation in Degenerative Arthritis, 434
- 4.5 Protein Oxidation in Muscle Wasting and Sarcopenia, 435
- 4.6 Protein Oxidation in Destructive Eye Diseases, 437
- 4.6.1 Age-Related Macular Degeneration, 437
 - 4.6.2 Cataract, 438
- 4.7 Protein Oxidation in Osteoporosis, 440
- 4.8 Protein Oxidation in Cancer, 441
- 4.8.1 Proteasome Inhibitors in Cancer Therapy, 444
- 4.9 Other Diseases, 446
- 4.9.1 Premature Aging Diseases Progeria and Werner's Syndrome, 446
 - 4.9.2 Renal Failure and Hemodialysis in Elderly People, 447
 - 4.9.3 Obesity, 447
 - 4.9.4 Idiopathic Pulmonary Fibrosis, 448
 - 4.9.5 Presbycusis (Age-Related Hear Loss), 448
- References, 448

List of Abbreviations 479

Index 493