

# Aging Mechanisms



Nozomu Mori • Inhee Mook-Jung  
Editors

# Aging Mechanisms

Longevity, Metabolism, and Brain Aging

 Springer

*Editors*

Nozomu Mori  
Department of Anatomy  
and Neurobiology  
Nagasaki University School of Medicine  
Nagasaki  
Japan

Inhee Mook-Jung  
Department of Biochemistry and Biomedical  
Sciences, College of Medicine  
Seoul National University  
Seoul  
South Korea

ISBN 978-4-431-55762-3

ISBN 978-4-431-55763-0 (eBook)

DOI 10.1007/978-4-431-55763-0

Library of Congress Control Number: 2015955138

Springer Tokyo Heidelberg New York Dordrecht London

© Springer Japan 2015

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

Springer Japan KK is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

# Preface

According to a predictive report on the increase in the elderly population in various countries, Japan and Korea are poised to become the world's top two nations, with constantly high elderly populations approaching 35–40 % in the latter half of this century. The rapidly aging populations in Japan and Korea promote movement toward a “senescent” society. Amazingly, however, if we examine the numbers of people living to over 100 years old, more than 60,000 centenarians currently reside in Japan. In Korea, the centenarian population is approximately 3,300, but it is estimated to grow to almost 40,000 by the year 2050. Japan and Korea are thus growing old so rapidly that we are indeed moving “into the unknown,” as described in a special report in *The Economist* several years ago (November 18, 2010). In such nations, research on aging is important not only sociologically but also biologically to understand the background of aging in our population.

During the last several decades, our knowledge concerning aging research has been growing rapidly. However, we are still far from achieving a complete understanding of the whole mechanism of aging: how we, as animals, age and how our lifespan is determined. Many researchers are working in this field in both Japan and Korea, and our scientific societies in relation to biomedical aging in the two countries have been interacting with each other. When one of the editors (N.M.) moved from the National Institute for Longevity Science (Research Institute, National Center for Geriatrics and Gerontology, Nagoya) to Nagasaki in 2006, we met on the small island of Ioujima in Nagasaki to discuss and exchange ideas on the basic science of aging. We called this discussion forum the “Asian Aging Core for Longevity” (AACL), and we have continued this series of AACL meetings for the last 10 years, alternating between Japan and Korea. In the last 5 years, it was supported by the Asian CORE program of the Japan Society for the Promotion of Science (JSPS). The studies described in this book were supported, at least in part, by the fund of the JSPS-Asian CORE program, through an intimate discussion at the AACL meetings.

This book was initially planned to summarize the aging research among all of the members of the AACL. However, owing to space and time limitations, we could not include the work of all the AACL members. The book is composed of a series of

topics in aging research which were explored through the daily dedicated laboratory work of our AACL members and their colleagues. Based on the topics of each manuscript, we, the editors, ordered each chapter such that the stories would facilitate the understanding of the scientific outcomes of our latest research on aging from the basic biology of longevity, metabolism, and brain aging with the goal of developing potential therapeutics for age-related diseases, such as Alzheimer's.

For convenience, we subdivided the chapters into seven parts. Part I provides an overview and re-investigation of various hypotheses of aging. Part II introduces studies of centenarians and cells of progeria patients. Part III discusses the usefulness of induced pluripotent stem (iPS) cells and primary cultured neurons for the study of aging and further explores the potentials of using lower organisms, such as budding yeast and nematodes, for the study of longevity and as a model for neurodegenerative disorders. Part IV introduces several key regulatory factors affecting tissue aging, such as  $\alpha$ -Klotho, FOXO transcription factors, neuropeptide Y, uremic toxins, and vitamin K. Part V describes the studies of the physiological nature of brain aging. It includes how aging affects potentials of adult neurogenesis in the hippocampus, signaling molecules for cognitive decline, neuroplasticity in the hippocampus and the cerebellum, and volume analysis of aging brains using a large brain database. Part VI addresses the pathophysiology of the aged brain. Alzheimer's disease (AD) is the most debilitating disease in the elderly. The processing mechanisms of amyloid precursor protein (APP), the accumulation and aggregation of amyloid- $\beta$ , and its degradation mechanisms are discussed here. A novel approach exploring new biomarkers of AD is also discussed. Finally, Part VII explores issues of antiaging, particularly focusing on therapeutic approaches for neurodegenerative diseases, including AD and polyglutamine diseases.

How do we age, and how is longevity determined? These questions are fundamental issues in biology. Solving the mechanisms of biological aging and the determination of longevity is not easy and may never be completely achieved. However, the studies described in this book are on the cutting edge of the science of biological mechanisms for each aspect of the biology of aging. We hope this book will be useful for researchers and graduate students in the field worldwide.

At this point, we would like to express our sincere thanks to all the authors for their valuable contributions to this volume. We are also grateful to Dr. Sang Chul Park, Dr. Eun Seong Hwang, Dr. Isao Shimokawa, and Dr. Yong-Sun Kim for their cooperation and encouragement during the course of our past meetings of the JSPS-AACL. Finally, we would like to thank Ms. Kanako Ishimaru and Ms. Noriko Tominari for their excellent secretarial assistance throughout the course of all the AACL meetings and also for putting this book together for final publication.

Nagasaki, Japan  
Seoul, South Korea

Nozomu Mori  
Inhee Mook-Jung

# Contents

## Part I From Hypotheses to Mechanisms

<b>1 The Biological Mechanisms of Aging: A Historical and Critical Overview</b> . . . . .	3
Sataro Goto	

## Part II Human Longevity: Centenarianism and Progeria

<b>2 Centenarian Studies: An Interdisciplinary Research on Healthy Longevity</b> . . . . .	31
Yasumichi Arai, Michiyo Takayama, Hiroki Inagaki, Yasuyuki Gondo, Yukie Masui, and Nobuyoshi Hirose	
<b>3 Progeria and Genome Instability</b> . . . . .	51
Fanbiao Meng, Baohua Liu, and Zhongjun Zhou	

## Part III Stem Cells, Cultured Neurons, and Lower Animal Models

<b>4 Use of Induced Pluripotent Stem Cells in Aging Research</b> . . . . .	67
Ken-ichi Isobe	
<b>5 In Vitro Aging Revisited: The Longevity of Cultured Neurons</b> . . . . .	79
Nozomu Mori	
<b>6 Cellular Longevity of Budding Yeast During Replicative and Chronological Aging</b> . . . . .	89
Kyung-Mi Choi and Cheol-Koo Lee	
<b>7 Oxidative Stress and <i>C. elegans</i> Models</b> . . . . .	111
Naoaki Ishii, Takamasa Ishii, and Philip S. Hartman	

<b>8</b>	<b>Genes and Pathways That Influence Longevity in <i>Caenorhabditis elegans</i></b> . . . . .	123
	Yujin Lee, Seon Woo A. An, Murat Artan, Mihwa Seo, Ara B. Hwang, Dae-Eun Jeong, Heehwa G. Son, Wooseon Hwang, Dongyeop Lee, Keunhee Seo, Ozlem Altintas, Sangsoon Park, and Seung-Jae V. Lee	
<b>9</b>	<b>Aging-Related Neurodegenerative Diseases in <i>Caenorhabditis elegans</i></b> . . . . .	171
	Dong Kyu Kim and Seung-Jae Lee	
<b>Part IV Metabolism: Factors Affecting Tissue Aging</b>		
<b>10</b>	<b><math>\alpha</math>-Klotho in Health and Diseases</b> . . . . .	183
	Yo-ichi Nabeshima	
<b>11</b>	<b>Role of the Forkhead Box O Family and Neuropeptide Y in Calorie Restriction</b> . . . . .	199
	Ryoichi Mori, Seongjoon Park, and Isao Shimokawa	
<b>12</b>	<b>Oxidative Stress and Endoplasmic Reticulum Stress in Kidney Aging: Impact of Uremic Toxins as the Cause of Stress</b> . . . . .	209
	Reiko Inagi	
<b>13</b>	<b>Vitamin K Benefits in Aging and Cancer</b> . . . . .	223
	Kotaro Azuma and Satoshi Inoue	
<b>Part V Aging Brain: Adult Neurogenesis, Synaptic Plasticity, and Brain Volume</b>		
<b>14</b>	<b>Insights into Aging of the Hippocampus: A View from the Topographic Differentiation</b> . . . . .	243
	Shozo Jinno	
<b>15</b>	<b>Knowledge of Signal Transduction Provides an Approach to Attacking Memory Decline</b> . . . . .	257
	Shuichi Yanai and Shogo Endo	
<b>16</b>	<b>Critical Roles of Oxidative Signals in Age-Related Decline of Cerebellar Synaptic Plasticity</b> . . . . .	275
	Sho Kakizawa and Nozomu Mori	
<b>17</b>	<b>Brain Aging Using Large Brain MRI Database</b> . . . . .	291
	Yasuyuki Taki	
<b>Part VI Aged Brain: Mechanisms of Neurodegeneration</b>		
<b>18</b>	<b>Brain Aging as a Cause of Alzheimer's Disease</b> . . . . .	305
	Toshiharu Suzuki, Ayano Kimura, Kyoko Chiba, Tadashi Nakaya, and Saori Hata	



<b>19 Catabolism and Anabolism of Amyloid-<math>\beta</math></b> . . . . .	319
Shoko Hashimoto, Per Nilsson, and Takaomi C. Saido	
<b>20 Biomarkers in Alzheimer's Disease: From Pathogenic Initiation to Downstream Outcomes</b> . . . . .	341
Sun-Ho Han, Jong-Chan Park, and Inhee Mook-Jung	
<b>Part VII Anti-brain Aging: Neuroprotection and Therapeutic Approaches</b>	
<b>21 Potentiation of Cellular Defense Capacity by Phytochemicals Activating NF-E2-Related Factor 2 for the Prevention and/or Treatment of Alzheimer's Disease</b> . . . . .	357
Gyu Hwan Park and Jung-Hee Jang	
<b>22 Immunotherapeutic Approaches Against Amyloid-<math>\beta</math> in Drug Discovery for Alzheimer's Disease</b> . . . . .	395
Seung-Hoon Yang, Jiyeon Kim, and YoungSoo Kim	
<b>23 Therapeutics for Polyglutamine Diseases Through Protein Degradation Pathway: Targeting the Nucleus</b> . . . . .	417
Atsushi Iwata	
<b>Name Index</b> . . . . .	431
<b>Subject Index</b> . . . . .	433



# Contributors

**Yasumichi Arai** Center for Supercentenarian Research, Keio University School of Medicine, Shinjuku, Tokyo 160-8582, Japan

[yasumich@keio.jp](mailto:yasumich@keio.jp)

**Shogo Endo** Memory Neuroscience, Aging Neuroscience Research Team, Tokyo Metropolitan Institute of Gerontology, Sakae-cho 35-2, Itabashi, Tokyo 173-0015, Japan

[sendo@tmig.or.jp](mailto:sendo@tmig.or.jp)

**Sataro Goto** Institute of Health and Sports Science & Medicine, Juntendo University Graduate School, Inzaishi, Chiba 270-1695, Japan

[sgotou@juntendo.ac.jp](mailto:sgotou@juntendo.ac.jp)

**Reiko Inagi** Division of Chronic Kidney Disease Pathophysiology, The University of Tokyo, Graduate School of Medicine, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[inagi-npr@umin.ac.jp](mailto:inagi-npr@umin.ac.jp)

**Satoshi Inoue** Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[INOUE-GER@h.u-tokyo.ac.jp](mailto:INOUE-GER@h.u-tokyo.ac.jp)

**Naoaki Ishii** Department of Molecular Life Science, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan

[nishii@is.icc.u-tokai.ac.jp](mailto:nishii@is.icc.u-tokai.ac.jp)

**Ken-ichi Isobe** Department of Immunology, Nagoya University Graduate School of Medicine, Tsurumai, Showa-ku, Nagoya 466-8550, Japan

[kisobe@med.nagoya-u.ac.jp](mailto:kisobe@med.nagoya-u.ac.jp)

**Atsushi Iwata** Department of Neurology, Graduate School of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[iwata-ky@umin.ac.jp](mailto:iwata-ky@umin.ac.jp)

**Jung-Hee Jang** Department of Pharmacology, School of Medicine, Keimyung University, Daegu 704-701, South Korea  
[pamy202@kmu.ac.kr](mailto:pamy202@kmu.ac.kr)

**Shozo Jinno** Department of Anatomy and Neuroscience, Graduate School of Medical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan  
[sjinno@med.kyushu-u.ac.jp](mailto:sjinno@med.kyushu-u.ac.jp)

**Sho Kakizawa** Department of Biological Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan  
[sho-kaki@pharm.kyoto-u.ac.jp](mailto:sho-kaki@pharm.kyoto-u.ac.jp)

**YoungSoo Kim** Center for Neuro-Medicine, Brain Science Institute, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul, Republic of Korea

**Cheol-Koo Lee** Division of Biotechnology, College of Life Sciences and Biotechnology, Korea University, Seoul 136-701, Republic of Korea  
[cklee2005@korea.ac.kr](mailto:cklee2005@korea.ac.kr)

**Seung-Jae Lee** Neuroscience Research Institute and Department of Medicine, Seoul National University College of Medicine, Seoul 110-799, Korea  
[Sjlee66@snu.ac.kr](mailto:Sjlee66@snu.ac.kr)

**Seung-Jae V. Lee** Department of Life Sciences, Pohang University of Science and Technology, Pohang, Gyeongbuk, South Korea

**Baohua Liu** Health Science Center, Shenzhen University, Shenzhen, China  
[ppliew@szu.edu.cn](mailto:ppliew@szu.edu.cn)

**Inhee Mook-Jung** Department of Biochemistry and Biomedical Sciences, College of Medicine, Seoul National University, Seoul 110-799, South Korea  
[inhee@snu.ac.kr](mailto:inhee@snu.ac.kr)

**Nozomu Mori** Department of Anatomy and Neurobiology, Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan  
[morinosm@nagasaki-u.ac.jp](mailto:morinosm@nagasaki-u.ac.jp)

**Yo-ichi Nabeshima** Laboratory of Molecular Life Science Foundation for Biomedical Research and Innovation, Kobe, Japan  
[nabemr@lmls-kobe.org](mailto:nabemr@lmls-kobe.org)

**Takaomi C. Saido** Laboratory for Proteolytic Neuroscience, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan  
[saido@brain.riken.jp](mailto:saido@brain.riken.jp)

**Isao Shimokawa** Department of Pathology, Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan  
[shimo@nagasaki-u.ac.jp](mailto:shimo@nagasaki-u.ac.jp)

**Toshiharu Suzuki** Laboratory of Neuroscience, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan  
[tsuzuki@pharm.hokudai.ac.jp](mailto:tsuzuki@pharm.hokudai.ac.jp)

**Yasuyuki Taki** Department of Nuclear Medicine & Radiology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryō-cho, Aoba-ku, Sendai 980-8575, Japan  
[ytaki@idac.tohoku.ac.jp](mailto:ytaki@idac.tohoku.ac.jp)

**Zhongjun Zhou** Department of Biochemistry, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong  
[zhongjun@hku.hk](mailto:zhongjun@hku.hk)

