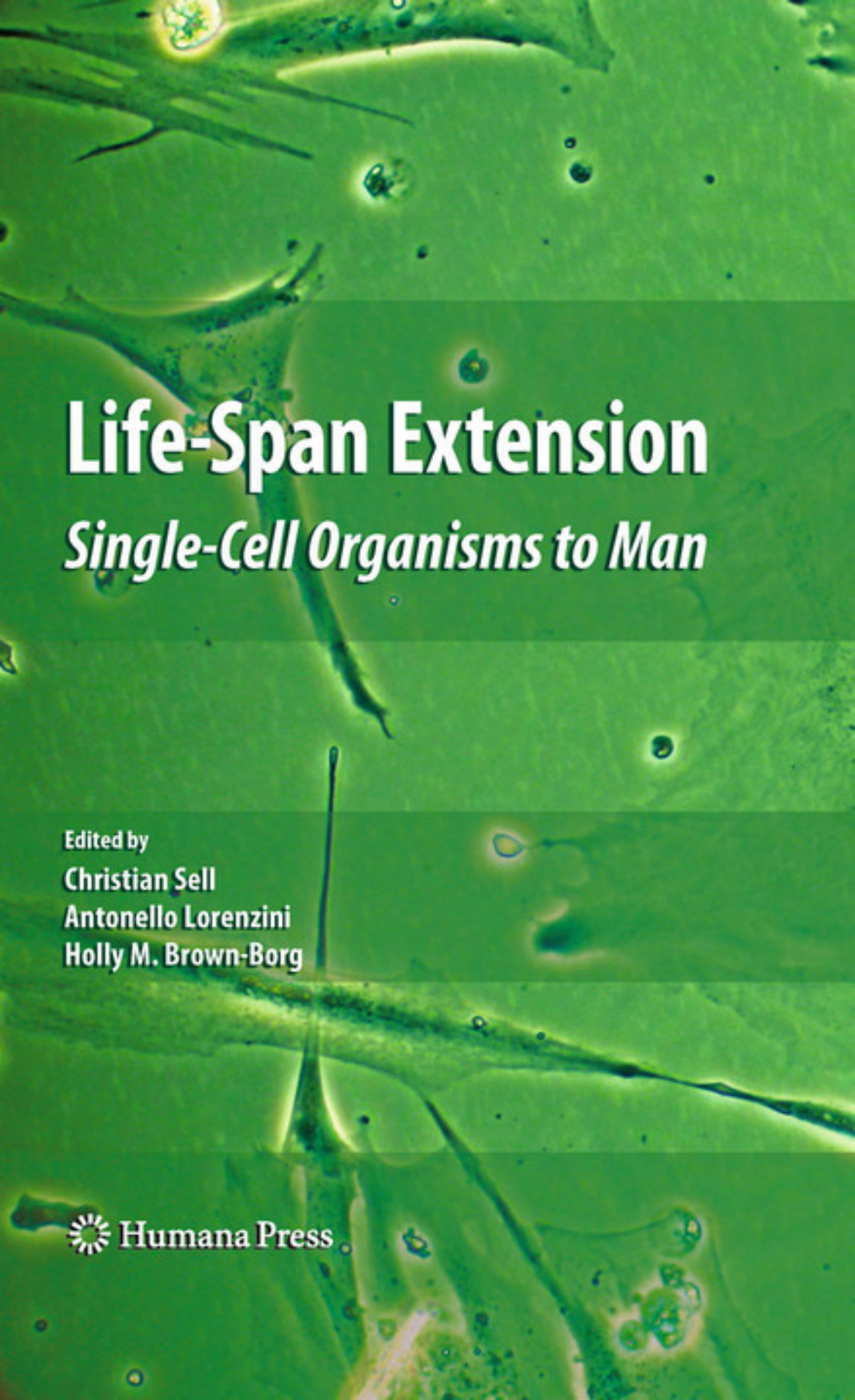
Life-Span Extension
Single-Cell Organisms to Man
Edited by
Christian Sell
Antonello Lorenzini
Holly M. Brown-Borg
Humana Press

Aging Medicine

Robert Pignolo, MD, PhD; Mary Ann Forciea, MD;
Jerry C. Johnson, MD, Series Editors

For other titles published in this series, go to
www.springer.com/series/7622

Life-Span Extension

Single-Cell Organisms to Man

Edited by

Christian Sell, PhD
Department of Pathology and Laboratory Medicine
Drexel University College of Medicine, Philadelphia, PA, USA

Antonello Lorenzini, PhD
Department of Pathology, and Laboratory Medicine
Drexel University College of Medicine, Philadelphia, PA, USA

Holly M. Brown-Borg, PhD
Department of Pharmacology, Physiology and Therapeutics
School of Medicine and Health Sciences, University of North Dakota
Grand Forks, ND, USA

Humana Press

Editors
Christian Sell
Department of Pathology
and Laboratory Medicine
Drexel University
College of Medicine
Philadelphia, PA
USA

Antonello Lorenzini
Department of Pathology
and Laboratory Medicine
Drexel University
College of Medicine
Philadelphia, PA
USA

Holly M. Brown-Borg
Department of Pharmacology,
Physiology and Therapeutics
School of Medicine and Health Sciences
University of North Dakota
Grand Forks, ND
USA

ISBN: 978-1-60327-506-4 e-ISBN: 978-1-60327-507-1
DOI 10.1007/978-1-60327-507-1
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009922206

Cover illustration: Christian Sell, PhD

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

This volume contains viewpoints of investigators studying the aging process in species ranging from yeast to man. The effort to compile these viewpoints has been driven by recent, remarkable discoveries about the underlying mechanisms important to aging. Single mutations that extend life span have been identified in yeast, worms, flies, and mice. Studies in humans have identified potentially important markers for successful aging. The genes and pathways identified in these studies involve a surprisingly small set of conserved functions, most of which have been the focus of aging research for some time. For example, recent genome-wide analyses of genes involved in life-span extension that are common to yeast and *Caenorhabditis elegans* identified a regulator of protein synthesis, the mTOR pathway, which leads to transcriptional control as a common longevity pathway in these two organisms. In mammals, this pathway intersects with neuroendocrine pathways and with the insulin/insulin-like growth factor (IGF) pathways, which have been identified as major modulators of life span and aging in both invertebrates and mice. Interestingly, both these pathways interact with stress responses to alter activity in response to environmental conditions. Thus, the emerging technologies and wide variety of systems that are now used to study aging and the mechanisms of aging provide enormous opportunities for the identification of common pathways that modulate longevity. It is these common pathways that are the focus of this volume.

Christian Sell — Philadelphia, PA
Antonello Lorenzini — Philadelphia, PA
Holly M. Brown-Borg — Grand Forks, ND

Contents

Contributors

Robert Arking
Department of Biological Sciences and Institute of Gerontology, Wayne State University, Detroit, MI, USA

Marta Artal-Sanz
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion, Crete, Greece

Elena Bellavista
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Kurt E. Borg
School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND, USA

Éric Le Bourg
Université Paul-Sabatier Centre de Recherche sur la Cognition Animale, Toulouse, France

Holly M. Brown-Borg
School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND, USA

Rochelle Buffenstein
The Sam and Ann Barshop Institute for Longevity and Aging Studies and Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Miriam Capri
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Laura Celani
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Alessandro Cellerino
Fritz-Lipmann Institute for Age Research, Beutenbergstr.11, Jena, Germany.

Elisa Cevenini
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Sean P. Curran
Department of Molecular Biology, Massachusetts General Hospital,
and Department of Genetics, Harvard Medical School, Boston, MA, USA

Yael H. Edrey
The Sam and Ann Barshop Institute for Longevity and Aging Studies
and the Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Claudio Franceschi
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Catia Lanzarini
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Francesco Lescai
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Valter D. Longo
Andrus Gerontology Center and Department of Biological Sciences,
University of Southern California, Los Angeles, CA, USA

Stella Lukas
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Edward J. Masoro
The Sam and Ann Barshop Institute for Longevity and Aging Studies,
University of Texas Health Science Center, San Antonio, TX, USA

Michelle E. Matzko
Center for Developmental and Health Genetics, The Pennsylvania State University, University Park, PA, USA

Roger J. McCarter
Center for Developmental and Health Genetics, The Pennsylvania State University, University Park, PA, USA

Daniela Monti
Department of Experimental Pathology and Oncology, University of Florence, Florence, Italy

Sharlene G. Rakoczy
School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND, USA

Stefano Salvioli
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Christian Sell
Department of Pathology and Laboratory Medicine, Drexel University College of Medicine, Philadelphia, PA, USA

Federica Sevini
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Sunita Sharma
School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND, USA

Nektarios Tavernarakis
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion, Crete, Greece

Paolo Tieri
Department of Experimental Pathology, University of Bologna, Bologna, Italy
C.I.G.-Interdepartmental Centre "L. Galvani," University of Bologna, Bologna, Italy

Introduction

Christian Sell

Keywords Aging • life span • evolution • nutrient • stress

Abbreviations DMBA: Dimethylbenzanthracene; IGF: Insulin-like growth factor mTOR: Mammalian target of rapamycin

1 Introduction

The chapters presented in this book deal with a variety of species and approaches to research into the basic mechanisms of aging. Placing such a broad collection into perspective can be difficult for those who are new to the area. This introduction provides background and perspective on the aging process. First, two terms that are widely used in aging research, aging and life span, are discussed because the usage and implications of these two terms are important to understanding research related to aging. Next, a conceptual framework is discussed that may provide a useful approach to organizing the information presented in the various chapters regarding multiple influences on longevity.

2 Aging vs. Life Span

In considering the impact of gene mutations on aging and life span, it is important to clarify the difference between these two terms. Considerable confusion exists in the general public and, to some degree, in the scientific community regarding the precise usage of the terms aging and life span *(1)*. A potentially useful distinction may be made if one considers that aging occurs within a given population. The term aging refers to the constellation of changes that occurs during the later stages of the life span of any species. Although broad, one potentially useful description of the phenotypic effects of these changes is that an aging organism shows a reduced capacity to maintain homeostasis. This description encompasses most if not all of the characteristics associated with aging such as reduced functional capacity,

increased vulnerability to multiple diseases, and a reduction in the ability to respond to stress or injury. Thus, gene mutations or environmental factors such as caloric restriction that have been found to delay the aging process provide improvements in a specific set of cellular or physiologic parameters late in life relative to control populations.

The term life span can be used in several contexts. It can refer either to the life span of a given population under study or to the species life span. Changes in the rate of aging can affect the life span of the study population but may not influence species life span. Species life span remains fixed within a certain limit, although what this limit may be is a matter of some debate *(2, 3)*. For example, caloric restriction will increase the life span of a given population but has not been shown to affect the life span of the species. Thus, there are two key questions concerning life span: *(1)* What mechanisms influence population life span and *(2)* what mechanisms determine the life-span characteristic of a species. These are two different questions. Most of the chapters in this volume deal with population life span. Only those that deal with the comparative biology of aging address the issue of differences between species.

A discussion of aging and its manifestations is provided by Dr. Arking in his chapter, "Overview of the Genetic Architecture of Aging." Dr. Arking provides a detailed analysis of differing life-span curves, indicating that multiple mechanisms underlie changes in life span. It seems to be the complex relationship between environmental influences and the response of the organism to these influences that culminate in the life-span characteristic of a given population. Given the complexity of interactions that dictate life span, it is surprising that common mechanisms would be apparent between divergent species. Recent evidence demonstrates commonalities in the functional pathways (at the level of both the cell and the organism) that respond to environmental influences that are ultimately responsible for life-span changes. Both targeted interventions, such as caloric restriction and gene manipulation, have identified what appear to be general pathways with the ability to modulate life span.

When discussing pathways that modulate aging and life span, one framework that might be useful for the layperson would be to group these pathways into general categories based on the timing of their response to environmental changes. The first category would be rapidly responding pathways. These pathways are involved in the response of the organism to acute stress (such as oxidation), toxicity, and damage; the second category of pathways would be moderately responding pathways, such as those that react more slowly to changes in environmental factors such as nutrient availability; the third category would be slowly responding pathways. This third category includes pathways critical for genomic integrity and other basic functions that would not be expected to undergo rapid alterations. Pathways in all three categories are essential for the organism and may respond to evolutionary pressures to produce a given phenotype.

Examples of rapidly responding pathways are discussed by Dr. Le Bourg. Multiple forms of mild stress such as hypergravity can increase life span in

Drosophila melanogaster. Although the mechanisms are not well understood, they include heat shock factors such as hsp70. The response to mild stress is rapid, yet it serves to produce an extension in life span that is a secondary outcome of the primary response.

One could also include the oxygen scavenging enzymes central to free radical theories of aging [see Muller et al. *(4)* for review] and the phase 1 detoxification enzymes in the first category of pathways. The phase 1 enzymes include the heme-containing cytochrome P450 family of enzymes, a large family of enzymes involved in the removal of hydrophobic chemicals from the organism as well as several biosynthetic pathways including cholesterol and bile acid synthesis *(5)*. The expression of the P450 enzymes is affected by exposure to toxins, and altered expression of a subset of the cytochrome P450 enzymes has been described in long-lived, growth hormone-deficient mouse strains *(6)*. It must be borne in mind, however, that the cytochrome P450 enzymes act not only to remove xenobiotics but also to activate carcinogens such as DMBA, creating reactive intermediates. Increased production of such reactive intermediates may increase cancer incidence and contribute to tissue damage. Thus the involvement of this system in modulating life span is likely to be complex [see Nebert and Dalton *(5)* for a discussion of this area].

The second category of pathways includes the neuroendocrine axis (growth hormone, IGF) and the mTOR pathway. These pathways have been the subject of considerable interest in the aging community in recent years. The chapters contributed by Drs. Brown-Borg et al., Matzko et al., and Longo consider this second category of pathways. Acting through mechanisms that are not yet completely clear, it seems that nutrient intake interacts with an organism's developmental program to accelerate or delay development, depending on the relative abundance of food. The highly conserved natures of the pathways that respond to changes in nutrient status reflect the basic need of all organisms for energy input.

The chapter by Dr. Tavernarakis and colleague explores the conserved nature in nematodes of the relationship between energy utilization, cell signaling, and life span. The suggestion that a shift in metabolic pathways that can be triggered by several cues, such as caloric restriction and nutrient sensing, is intriguing when considered alongside the chapters dealing with longevity in mammals. Do such metabolic shifts underlie the hormetic response that is suggested by Drs. Matzko and company and are they at play in the long-lived animals described by Brown–Borg et al.? In a larger context, the balance that is struck between energy intake and fecundity is consistent with evolutionary theories of aging *(7, 8)*.

Examples of the third category of pathways that appear to modulate changes in life span/aging include those involved in DNA damage repair, cell cycle checkpoints, senescence, and apoptosis. These fundamental cellular mechanisms would not be predicted to vary greatly in response to immediate environmental influences, yet they are widely believed to be important in aging. The evidence that genomic integrity is important to aging and life span depends primarily on the reduction in life span and rapid senescence phenotypes that result from mutations in proteins

involved in genomic maintenance. Werner's syndrome is an excellent example of a mutation, in this case a DNA helicase, involved with DNA damage response and genome stability, and ultimately important for life span *(9)*. Other examples include the accelerated aging caused by a reduction in the levels of Ku 80, a protein critical to nonhomologous end joining *(10)* or increased activity of p53 *(11)*. This third category of pathways may be less responsive to environmental influences than are the first two categories and is part of the cellular maintenance mechanism that is required for normal life span.

3 Environmental Pressures That Modulate Life Span

The external triggers that induce the responses outlined above are numerous. Experimentally, stresses such as low nutrient availability and mild stresses such as heat shock or low-level radiation in *D. melanogaster* are paradigms for extending life span. Dr. Longo shows that blunting the intracellular pathways central to nutrient sensing can lead to life-span extension in yeast that are in a stable, growth-arrested state. Similar pathways seem to be involved in the response of mice to caloric restriction but, as would be expected in a multicellular organism, the response is multifaceted. The complexity of the response to caloric restriction in rodents and its relationship to response to stress are explored in the chapter by Matzko, McCarter, and Masoro. The overall picture that seems to emerge is that population life span is influenced by stress responses that can be influenced by a number of external signals and act through a set of conserved intracellular pathways. One intriguing question is the nature of the relationship of these responses, if any, to species life span. We would predict that species life span is molded by response to environmental influences resulting in the establishment of an aging trajectory that is characteristic for a given species. The mechanisms that drive this process and their relationship to the interventional studies that modulate life span in a specific species and experimental setting are, however, unclear. The chapters contributed by Dr. Buffenstein deal with a comparative approach to aging that seeks to address these questions. Specifically, what are the fundamental mechanisms that lead to species-specific differences in life span? The difficult task of identifying these mechanisms requires the type of comparative analysis involving animals such as the extraordinary naked mole-rat. These models, combined with the advent of more advanced techniques for comparative analysis, will provide information regarding these mechanisms.

In summary, the field of aging is expanding exponentially with extraordinary advances coming from multiple approaches. We hope that the collection of viewpoints assembled here will provide insight and food for thought to those interested in this area.

Acknowledgments We sincerely thank all the authors for their wonderful contributions and patience during the production process. Finally, we thank Pam Fried and Diana Winters for their tireless work in copyediting the manuscripts.

References

1. Lithgow GJ. Why aging isn't regulated: A lamentation on the use of language in aging literature. Exp Gerontol 2006;41:890–3.
2. Butler RN, Warner HR, Williams TF, et al. The aging factor in health and disease: the promise of basic research on aging. Aging Clin Exp Res 2004;16:104–11; discussion 11–2.
3. Warner H, Anderson J, Austad S, et al. Science fact and the SENS agenda. What can we reasonably expect from ageing research? EMBO Rep 2005;6:1006–8.
4. Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. Trends in oxidative aging theories. Free Radic Biol Med 2007;43:477–503.
5. Nebert DW, Dalton TP. The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nat Rev Cancer 2006;6:947–60.
6. Amador-Noguez D, Dean A, Huang W, Setchell K, Moore D, Darlington G. Alterations in xenobiotic metabolism in the long-lived Little mice. Aging Cell 2007;6:453–70.
7. Kirkwood TB, Austad SN. Why do we age? Nature 2000;408:233–8.
8. Hughes KA, Reynolds RM. Evolutionary and mechanistic theories of aging. Annu Rev Entomol 2005;50:421–45.
9. Kudlow BA, Kennedy BK, Monnat RJ, Jr. Werner and Hutchinson-Gilford progeria syndromes: Mechanistic basis of human progeroid diseases. Nat Rev Mol Cell Biol 2007;8:394–404.
10. Li H, Vogel H, Holcomb VB, Gu Y, Hasty P. Deletion of Ku70, Ku80, or both causes early aging without substantially increased cancer. Mol Cell Biol 2007;27:8205–14.
11. Campisi J. Aging and cancer cell biology. Aging Cell 2008;7:281–4.