Protein Metabolism and Homeostasis in Aging

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DEDICATION

To my father

PREFACE

Aging is loosely defined as the accumulation of changes in an organism over time. At the cellular level such changes are distinct and multidimensional: DNA replication ceases, cells stop dividing, they become senescent and eventually die. DNA metabolism and chromosomal maintenance, together with protein metabolism are critical in the aging process. The focus of this book is on the role of protein metabolism and homeostasis in aging. An overview is provided of the current knowledge in the area, including protein synthesis, accuracy and repair, post-translational modifications, degradation and turnover, and how they define and influence aging. The chapters mainly focus on well-characterised factors and pathways, but new areas are also presented, where associations with aging are just being elucidated by current experimental data.

Protein turnover, the balance between protein synthesis and protein degradation is carefully maintained in healthy cells. Chapters 1 and 2 illustrate that aging cells are characterised by alterations in the rate, level and accuracy of protein synthesis compared to young ones, and that mRNA translation, essential for cell growth and survival, is controlled at multiple levels. The theory that growth and somatic maintenance are believed to be antagonistic processes is described in Chapter 3: inhibition of protein synthesis results in decreased rates of growth and development, but also confers an extension of lifespan, as shown for example by the effects of dietary restriction in various models organisms. Quality control mechanisms ensure misfolded or damaged proteins are remodelled or repaired, but when this fails proteins are targeted to go through degradation, in order to avoid untimely cell death. The ubiquitin/proteasome system keeps cells clear of abnormal, damaged or denatured proteins (detailed in Chapter 4), while autophagy degrades long-lived proteins and small organelles (presented in Chapter 5); compromised activity of both processes has been tightly correlated to aging. Accumulation of damaged or misfolded proteins within cells has been associated with human age-related, neurodegenerative diseases. The paradoxical situation of autophagy up-regulation in models of premature aging is also discussed in Chapter 6.

The insulin/IGF-1, TGFβ, TOR and p38/ MAP kinase signalling pathways play a part in regulating protein turnover and have been linked to aging through a number of their components, discussed in Chapter 7. Inhibition of the insulin/IGF and TOR pathways results in lifespan extension in worms, as detailed in Chapter 8, similarly with other longevity pathways, including dietary intake and mitochondrial

function. The role of mitochondria in protein quality control and the influence of reactive oxygen species in aging are presented in detail in Chapter 9. Chapter 10 discusses that different types of stress, intracellular, oncogenic and environmental, such as food and space restrictions, oxidative stress, temperature fluctuations and accumulation of damaged proteins, have been shown to induce premature aging and/or senescence through mechanisms independent of telomere shortening. In Chapter 11 the free radical and oxidative stress theories of aging are portrayed to link such stress factors to the occurrence of aging through the function of mitochondria, the activity of detoxifying enzymes and degradation pathways and their effects on protein turnover, while resistance to stress has been directly associated to lifespan extension and delayed aging in model organisms. Stress is also a major inducer of the sumoylation pathway, a post-translational protein modification that, together with substrate interactions with other ubiquitin-like proteins, show differential activity in aging tissues and has recently been linked to the onset of cellular senescence; these pathways are presented in detail in Chapters 12 and 13. The critical importance of maintaining cell homeostasis infuses through every chapter in this book, but is presented in more detail in Chapter 14, especially focusing on hormone signalling in response to environmental cues. Hormones and cytokines that affect muscle homeostasis during ageing are presented in Chapter 15. The main pathways that take part in skeletal muscle atrophy and regeneration are illustrated, followed by a description of current gene and cell therapies to rescue muscle atrophy and wasting. The book concludes with Chapter 16, where common techniques used in protein metabolism and homeostasis research are presented and critically reviewed.

We would like to thank all the authors of this book for excellent contributions, and hope that the reader will enjoy reading the chapters and be inspired to further their knowledge into this ever-expanding and exciting field. As the advances of modern technology and medicine have significantly raised the life expectancy of the population, it is becoming ever more important to gain a deeper insight and understanding of the mechanisms that influence the aging process. Such knowledge is an essential prerequisite for the development of effective strategies aiming to increase health span and quality of life for the elderly.

Artemis Andreou
Nektarios Tavernarakis
March 2010, Heraklion, Greece

ABOUT THE EDITOR...

NEKTARIOS TAVERNARAKIS is a Research Director (Professor) at the Institute of Molecular Biology and Biotechnology, in Heraklion, Crete, Greece, heading the *Caenorhabditis elegans* molecular genetics laboratory. He earned his PhD degree at the University of Crete, studying gene expression regulation in yeast, and trained in *C. elegans* genetics and molecular biology at Rutgers University, New Jersey, USA. His research focuses on studies of neuronal function and dysfunction, using the nematode *Caenorhabditis elegans* as a model organism. His main interests are the molecular mechanisms of necrotic cell death in neurodegeneration and senescent decline, the molecular mechanisms of sensory transduction and integration by the nervous system, the interplay between cellular metabolism and ageing, and the development of novel genetic tools for *C. elegans* research. He is the recipient of a European Research Council (ERC) Advanced Investigator grant award, a European Molecular Biology Organisation (EMBO) Young Investigator award, an International Human Frontier in Science Program Organization (HFSPO) long-term award, the Bodossaki Foundation Scientific Prize for Medicine and Biology, the Alexander von Humboldt Foundation, Friedrich Wilhelm Bessel research award, and is member of EMBO.