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# *Editorial*
# Cellular Models of Aging

**Paula Ludovico,[1,2] Heinz D. Osiewacz,[3] Vitor Costa,[4,5] and William C. Burhans[6]**

[1] *Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*
[2] *ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Portugal*
[3] *Department of Molecular Biosciences, Faculty of Biosciences and Cluster of Excellence Macromolecular Complexes, Johann Wolfgang Goethe-Universität Frankfurt, Max-von-Laue-Straße 9, 60438 Frankfurt, Germany*
[4] *Instituto de Biologia Molecular e Celular (IBMC), Universidade do Porto, Rua do Campo Alegre 823, 4150-180 Porto, Portugal*
[5] *Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal*
[6] *Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*

Correspondence should be addressed to Paula Ludovico, pludovico@ecsaude.uminho.pt

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Biological aging is a complex and multifactorial process driven by genetic, environmental, and stochastic factors that lead to the physiological decline of biological systems. In humans, old age is the most important risk factor for the development of degenerative diseases, some of which are severe (e.g., dementia, cancer). Understanding the basic mechanisms of aging is essential to the development of effective therapeutic interventions against age-related diseases.

Mechanisms of aging have been extensively investigated in various model organisms and systems. Although results obtained from studies with any model system should be viewed with caution when translated to human aging, much of the current understanding of conserved pathways involved in aging and lifespan control was obtained from studies that employed experimentally tractable models. Aging research has now reached a stage where it is possible to move from a reductionist approach studying individual factors towards a more global analysis. With the recent development of technologies that allow for the generation and computational analyses of large data sets, the ultimate goal is to unravel the various interacting molecular pathways governing aging and thus elaborate a holistic understanding of this complex process.

This special issue on was compiled with the following aims: (i) to enhance our understanding of *basic mechanisms* of aging and (ii) to investigate potential *interventions* into aging processes. Both original research articles as well as review articles provide an overview of current research and the status of experimentally accessible aging models.

A number of contributions describe the *molecular pathways* that are part of the network controlling aging and longevity. S.-H. Lee and colleagues analyzed the effect of overexpressing the two main components of fatty-acid $\beta$-oxidation and report that this genetic manipulation leads to lifespan extension of the corresponding *Drosophila* transgenic strains. They also show that the extension of lifespan mediated by caloric restriction (CR) becomes reduced in the newly investigated strains. This appears to be related to the activation of the dFOXO transcription factor, a known regulator involved in longevity control.

In an original research article S. Makpol and colleagues address the molecular mechanism of $\gamma$-tocotrienol (GTT) in preventing aging, focusing on its antiapoptotic effects in stress-induced premature senescence (SIPS) of human diploid fibroblasts (HDFs). Their results show that SIPS cells exhibit senescent-phenotypic characteristics that include increased expression of senescence-associated $\beta$-galactosidase and G0/G1 cell cycle arrest accompanied by telomere shortening and decreased telomerase activity. Their findings suggest that GTT inhibits apoptosis and delays cellular senescence of HDFs by inhibiting the intrinsic mitochondria-mediated apoptotic pathway.

In a review article, R. Gredilla and colleagues discuss the latest research on DNA repair in eukaryotes and its relevance

for aging. Their focus is on research using selected model systems and the role they can play in unraveling conserved pathways relevant to aging of mammals, including normal human aging and diseases arising from impairment of repair functions. In this paper the different pathways involved in repair of different kinds of lesions of both nuclear as well as mitochondrial DNA are covered.

A review article by J. C. Conde-Pérezprina and colleagues continues on the topic of DNA repair with a focus on highly conserved mismatch repair systems that are important for maintaining cellular homeostasis. A research article by S. Ohshima explores the interesting phenomenon of centrosome amplification, which occurs in replicatively aged fibroblasts and is often detected in cancer cells as well. This study describes a previously unknown link between supernumerary centrosomes and the tumor suppressor p53. A paper by M. Suzuki and colleagues addresses questions relevant to the amplification of DNA damage signals recently detected by the authors in irradiated normal human fibroblasts. Their study establishes connections between DNA damage signal amplification, sustained activation of ATM-p53 DNA damage response pathways, and replicative senescence.

The DNA damage response protein PARP1 is an important player in chromatin remodeling, DNA repair, telomere maintenance, resolution of replicative stress, and cell cycle control. A. Mangerich and A. Bürkle review in their paper the molecular mechanisms underlying the role of PARP1 in longevity and aging with special emphasis on cellular studies.

Some papers in this special issue describe new insights obtained from research aimed at understanding the impact of *environmental effects* on aging and longevity. This includes specific *interventions* on aging processes that involve the application of different compounds and environmental manipulations (such as CR) that affect the ability of individuals to survive long periods of environmental stress. The paper by L. Váchová and colleagues reviews the impact of processes occurring in colonies of the unicellular aging model *Saccharomyces cerevisiae*, which in the past was mostly viewed in the context of individual cells and as such, has been investigated as a model for replicative and chronological aging. In their paper the authors discuss the adaptive potential of a yeast population growing as a colony and the cellular processes that allow them to survive long periods of stress.

V. Palermo and colleagues also used the unicellular aging model *S. cerevisiae* to determine the effects of apples and their components, such as flesh, skin, and polyphenolic fractions on aging and oxidative stress. Their data point to a cooperative role of all apple components in promoting yeast chronological lifespan extension.

A review article by Y. Dong and colleagues explores the potential of therapeutic interventions designed to mitigate aging and age-related diseases using nutraceuticals from various plants. Their paper describes how these compounds modulate signaling pathways and can be effective in counteracting the development of various diseases. In their treatise they focus on knowledge gained from investigations with short-lived invertebrate models such as *Caenorhabditis elegans* and *Drosophila* species and discuss the need for more extensive research to unravel the mechanistic basis of the observed beneficial effects. They also emphasize that translational research directed toward demonstrating effects in humans is necessary.

In a review article, S. Ribaric discusses CR, a key environmental manipulation that has been shown to extend lifespan in a variety of aging model systems. The author has focused on adaptive stress responses and increased resistance to stress elicited by CR. These coordinated and adaptive stress responses act at the cellular and whole-organism level by modulating epigenetic mechanisms, signaling pathways regulating cell growth, and aging and cell-to-cell signaling molecules.

J. Santos and colleagues discuss in a review article the role of nutrient/energy signaling pathways in the regulation of yeast chronological lifespan. In particular, the authors focus on extrinsic factors that impact cellular longevity, such as culture medium, products of fermentation, and ammonium. How the modulation of TOR, Sch9, and Ras/protein kinase A nutrient signaling pathways is involved in longevity regulation by CR (glucose or amino acid), ethanol, acetic acid, and ammonium is also covered.

A number of contributions have addressed the role of *reactive oxygen species* (ROS) in the regulation of aging. P. Back and colleagues discuss in a review article recent findings relevant to the role of ROS in aging of the *C. elegans* model organism. The authors report on accumulating evidence that argues against the oxidative stress theory of aging and present an alternative theory, namely the redox signaling theory of aging. This theory proposes that ROS may promote longevity through the modulation of redox-sensitive proteins that control cellular metabolism and stress responses. The progressive prooxidizing shift in the redox state of the cell disrupts redox-regulated signaling mechanisms, leading to aging.

In a review article, N. Sampson and colleagues discuss current evidence highlighting the therapeutic potential of targeting the pro-oxidant shift in redox homeostasis for the treatment of age-related diseases associated with myofibroblast dysregulation. The prooxidant shift in redox homeostasis is mainly due to elevated production of NADPH oxidase 4-(NOX4-)derived hydrogen peroxide and is supported by a concomitant decrease in nitric oxide/cGMP signaling and ROS scavenging enzymes.

For years it has been known that in humans, physical exercise can duplicate the effects of CR, including the activation of oxidative stress defenses that ultimately lead to reduced levels of ROS and oxidative damage. G. Corbi and colleagues review the literature describing the underlying mechanisms, including those in which sirtuins that promote longevity play important roles.

In their original research article, M. Baraibar and colleagues describe an in silico approach to identifying molecular actors and cellular pathways affected by protein damage. A database of proteins modified by carbonylation, glycation, and lipid peroxidation products during aging and in age-related diseases was developed and compared to lists of proteins identified during cellular replicative senescence in vitro. Common cellular pathways that include enzymes

involved in intermediate metabolism were found to be targeted by these modifications.

In the view of the editors, the high quality contributions published in this special issue illuminate many important aspects of aging that have emerged from studies that employed a variety of cellular models in numerous laboratories in recent years. We are grateful to the authors for their contributions and for the opportunity to present their data and ideas in this issue. We hope that readers find these contributions as interesting and informative as we did while preparing this issue for publication.

*Paula Ludovico*
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