



Editorial

Biology of aging: Paving the way for healthy aging



The world population is aging, and the number of elderly persons is increasing, especially those over 85 years. This unprecedented increase is not without putting a huge burden on the society, either from a health or social perspective. There may be several answers to the related challenges. One of the most basic approaches is to better understand the biology of aging as major means to prevent, influence or delay the appearance of chronic, aging-associated diseases. This would mean that elderly persons may expect to extend their healthspan in conjunction with the functionspan.

Indeed, these last years the biology of aging made huge progresses towards a better understanding of the basic biological mechanisms of aging and summed up this knowledge by announcing the nine hallmarks of aging (López-Otín et al., 2013). These are the fundamental biological aspects which collectively influence the aging process leading to various chronic diseases: genomic instability, telomere attrition, epigenetic alteration, defective protein metabolism (proteostasis), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication. The description of these nine hallmarks do not preclude that there is a hierarchy among them, however from recent experimental data some of these hallmarks seem to be influencing more profoundly the biology of aging than the others. However, this picture may change in the future with the advancing of our understanding. Some of the major new directions in the biological research of aging are discussed/mentioned below.

Presently a huge experimental effort is put on studies elucidating the properties of senescent cells and the underlying process of cellular senescence (Tchkonia et al., 2013), aiming to understand their biological and pathological role. During the last years the understanding that the senescent cells are not inert but are actively contributing to the inflamm-aging process by their senescence-associated secretory phenotype (Demaria, 2017) made them the number one public target for attempts to modulate the biological aging process. The geroscience concept stating that because aging is the major risk factor for most non-genetic chronic diseases, an understanding of the role of aging in the onset of disease should open up new avenues for disease prevention and cures (Sierra, 2016). Thus, in accordance with this concept, senescent cells should be eliminated, and a family of drugs dubbed senolytics is being developed (Kirkland et al., 2017). This approach is meant to intervene in the age-related diseases by modulating aging itself, here understood as an accumulation of senescent cells.

One other major progress through these last years was the establishment of the idea, and then at least partial experimental proving of the existence of an epigenetic clock, which could explain the aging process and also help to distinguish between biological and

chronological aging (Horvath et al., 2015).

Finally, the advances of our understanding of the different aspects of the intercellular communication defects mentioned above, namely the immunosenescence and the inflamm-aging processes, helped us to understand various - until now somehow dislocated and unclear - aspects of aging. The new concept of immunoadaptation/remodeling made clear that changes in the properties of the immune systems observed during healthy aging are not exclusively detrimental but also clearly adaptive in the sense that these changes may serve to optimize the pathogen resistance of aging organisms, for example to increase the response to vaccination. The integration of concepts of immunobiography and trained innate immune memory into this overarching new concept of immunoadaptation/remodeling helps also to understand the changes in the immune system with aging by highlighting new interactions inside the immune system (Franceschi et al., 2017; Fulop et al., 2018).

In this spirit the 2nd Sherbrooke Biology of Aging Symposium was organised in Montreal on the 19–20 October 2016 convening together the leading scientists in the field, under the title of “Biology of Aging: Paving the way for healthy aging”. The symposium contained the following sessions: Session 1: Immunosenescence, Inflammation and Vaccination; Session 2: Longitudinal studies/cohort studies; Session 3: Stems cells/age-associated diseases/biomarkers; Session 4: Genetic and Epigenetics; Session 5: Cell senescence, metabolism, aging and cancer; Session 6: Cell metabolism, Diabetes and aging and Session 7: Aging, brain and dementia; and Session 8: Interventions – Geroscience. The present Special Edition of the Experimental Gerontology is devoted to the various papers issued from the Symposium. They are capturing the advances from the field of immunology, through stem cell biology to cell senescence and the epigenome. Several papers are addressing the biological aspects of some typical chronic diseases of aging such as the Alzheimer's disease and diabetes, with the aim to better understand the involvement of aging in their development and progression. Finally, some clues to interventions which can extend the healthy lifespan (healthspan), such as exercise or modified nutrition, are also included in this special volume. Finally, papers trying to capture the complexity of the aging process and the means to study it are also included in this issue.

Wang et al. in their research paper present evidence that 30% dietary restriction could significantly improve renal pathology and some metabolic characteristics. Their findings suggest that a 30% dietary restriction for 6 months can delay renal aging and reduce the accumulation of SASP by retarding the progression of DNA damage and decreasing the transcription activity of NF- κ B, thus providing a target to delay renal aging.

Cohen et al. focus on the risks for the analyses of biomarkers in epidemiological studies taking as an example of calcium. Recent studies have shown contradictory associations between calcium levels and health outcomes. Their study demonstrates that most biomarkers have multiple physiological roles and are implicated in multiple pathologies. Thus, epidemiological studies on age-related biomarkers should integrate the complex interrelations of the aging process.

Croteau et al. describe that brain undergoes structural atrophy and lower brain energy metabolism in MCI and AD measured by MRI and PET imaging and demonstrate that the deterioration in brain energy metabolism is specific to glucose. Their results suggest that a ketogenic intervention to increase energy availability for the brain is warranted in an attempt to delay further cognitive decline by compensating for the brain glucose deficit in MCI and AD.

Hurez et al. focus on age-related immune changes as they affect cancer immune surveillance, immunopathogenesis and immune therapy responses. They review the numerous factors which may affect successful immunotherapy in the aging organism and propose avenues to study them.

Reidy et al. describe the aging-related effects of bed rest followed by eccentric exercise rehabilitation on skeletal muscle macrophages and insulin sensitivity. Their data suggest that muscle macrophages are modulated as a result of exercise rehabilitation following bed rest and may be more associated with muscle regrowth/hypertrophy rather than insulin sensitivity in young or older adults.

Ferbeyre reviews the senescent cells accumulation with age and contribution to pathologies associated to old age. In cells forced to senesce by expression of oncogenes or short telomeres, aberrant activation of the ERK/MAP kinase signaling pathway lead to selective protein degradation by the ubiquitin proteasome system. The proteins affected by this process control key cellular processes known to be defective in senescent cells.

Frasca describes the role of senescent B cells in aging and in age-related diseases. Immune cells with a senescence-associated secretory phenotype increase in the blood of elderly individuals or individuals with age-associated diseases or with infections. The review focuses on senescent B cells, their increase in aging, age-associated conditions and infections. Similarities with other senescent immune cells are presented and discussed.

Le Page et al. describe the role of the innate immune system in the development of Alzheimer's disease. Microglia in the brain are innate immune cells, and brain-initiated inflammatory responses reflected in the periphery suggest that Alzheimer's disease is to some extent also a systemic inflammatory disease. Greater permeability of the blood brain barrier facilitates the transport of peripheral immune cells to the brain and vice versa so that a vicious circle originating on the periphery may contribute to the development of overt clinical AD.

Hares et al. present that the telomere length and the rate of telomere shortening have been suggested as particularly useful physiological biomarkers of the processes involved in senescent decline of somatic and reproductive function. They have tested the assumptions and predictions of the quasi-longitudinal approach using longitudinal telomere data in a wild cooperative mammal, the banded mongoose. Their results suggest that telomere dynamics in banded mongooses are more complex than is typically assumed, and that longitudinal studies across whole life spans are required to elucidate the link between telomere dynamics and senescence in natural populations.

He et al. discuss the need to elucidate the causal effects of common intermediate risk factors on the onset of age-related diseases for developing prevention and intervention procedures. They conducted two-stage time-to-event Mendelian randomization meta-analyses combining five large-scale longitudinal cohorts to investigate dynamic causal effects of cardiovascular disease risk factors on the age-at-onset of age-related diseases. Their findings have important implications in unraveling causal effects of common risk factors on age-related diseases and guiding effective intervention strategies to reduce the incidence of

these diseases.

Jazwinski et al. discuss the role of mitochondria as a central player in energy metabolism in the process of oxidative phosphorylation. Mitochondria also communicate with other subcellular compartments. They review another form of communication between the mitochondria and the nucleus, in which the dysfunction of the former triggers changes in the expression of nuclear genes to compensate for it. This compensation plays out differently in males and females, and variation in nuclear genes whose products affect mitochondrial function influences the outcome. Thus, the theme of mitochondria-nucleus communication as an adaptive response during aging appears very widespread.

Laatar et al. present a randomized controlled trial examined postural, physical and cognitive performances and postural performance during daily life tasks in older adults pre- and post- 6-months physical and physical-cognitive interventions. Results showed that only simultaneous physical-cognitive training enhances performance in daily life tasks, however after 3 months the benefice was lost, suggesting the need for regular interventions.

Xu and Larbi discuss the role of the immune system which protects the host from foreign pathogens. Inflammation is one of the key processes that alert the immune system but when loss of regulation occurs, a long-term chronic inflammation settles and is likely to be detrimental to the host. So the immune system and inflammation depending on their regulation/dysregulation may either be beneficial or detrimental. Interventions should take these aspects into consideration.

Tuttle and Maier present that within an aging population there is significant variation regarding extent of age related disease and functional impairment. This variability between individuals is thought to be expressed as biological age. They suggest that combining functional measures with molecular markers of biological age, could improve the current Comprehensive Geriatric Assessment by identifying individuals undergoing a rapid aging process. They describe the current knowledge and clinical utility for potential biomarkers of aging and their potential use in the future.

Martins et al. compared the effects of 12 weeks of high-intensity interval body weight training with combined training on insulin resistance and inflammatory markers in postmenopausal women at high risk of type 2 diabetes mellitus. Their study suggests that changes in HOMA, IL-1ra, 6MWT, and muscle mass index with high-intensity interval body weight training are similar when compared to combined training in postmenopausal women at high risk of T2DM.

Merani et al. present a study where they compared the antibody and T-cell responses in older adults randomized to receive high dose or standard dose influenza vaccine as well as determined whether cytomegalovirus (CMV) serostatus affects the response to vaccination and identified differences in the response to vaccination in those older adults who subsequently presented an influenza infection. Their study illustrates that high dose influenza vaccines have little impact on the development of functional T-cell memory in older adults. Furthermore, poor outcomes of influenza infection in older adults may be due to a strong IL-10 response to influenza following vaccination, and persistent CMV infection.

Rutenberget al. explore the mechanistic relationships between aging, frailty and mortality, by developing a computational model in which possible health attributes are represented by the nodes of a complex network, with the connections showing a scale-free distribution. Their model demonstrates the known patterns of frailty and mortality without any assumption of programmed aging. Their model permits a better understanding of factors that influence the health trajectories of individuals.

Molony et al. discuss that extended lifespan is associated with a progressive decline in immune function and a paradoxical state of low-grade, chronic inflammation that may contribute to susceptibility to viral infection, and reduced responses to vaccination. They specifically focus on age-related changes in key pattern recognition receptor signaling pathways, converging on altered cytokine responses, including a

notable impairment of antiviral interferon responses. They highlight an emergent change in innate immunity that arises during aging - the dampening of the dynamic range of responses to multiple sources of stimulation - which may underlie reduced efficiency of immune responses in aging.

Van Ramsdonk focuses on recent advances in aging research which have continued to increase our understanding of the aging process. Until the last couple of decades, aging was viewed as an inevitable process of damage accumulation and not a subject for scientific pursuit. He reviews experiments demonstrating the roles of genetics and epigenetics in modulating longevity and concludes with a new model of aging. This genetic switch model of aging proposes that aging is caused by a genetically-programmed turning off of survival and maintenance pathways after reproduction finishes leading to a progressive functional decline. If this model is correct, it may be possible to extend lifespan and healthspan by identifying the molecular pathways involved and simply turning the switch back on.

Richardson et al. describe a study with the aim to determine the actual movement velocity of high-velocity, low-load (HVLL) and low-velocity, high-load (LVHL) resistance exercise in a group of older adults. The protocols used provide a simple solution for exercise professionals to ensure that older adults are training at desired velocities when carrying out resistance exercise, without the need for equipment that measures velocity.

Yashin et al. performed GWAS of Alzheimer's disease in several study populations and investigate possible roles of detected genetic factors in developing AD hallmarks and in other health disorders. The results of analyses confirmed strong associations of genetic variants from well-known genes APOE, TOMM40, PVRL2 (NECTIN2), and APOC1 with AD. The evidence on genetic connections between AD and vulnerability to infection, as well as between AD and other health disorders, such as cancer and type 2 diabetes, were investigated. The progress in uncovering hidden heterogeneity in AD would be substantially facilitated if common mechanisms involved in development of AD, its hallmarks, and AD related chronic conditions were investigated in their mutual connection.

Witkowski et al. discuss that with cellular aging proteostasis progressively fails and proteostenosis occurs. There are several mechanisms involved in the modulation and protection of the proteome in the T cells which include mainly multiple layers of vesicle-bound and cytoplasmic proteases acting mostly by degradation of obsolete and age-modified proteins. Recently it was shown that another not yet so widely known system consisting of obligatorily calcium-dependent cysteine proteases, the calpains and their inhibitor, the calpastatin serves in T cells as a dual switch, either activating or inactivating different proteins depending on intracellular conditions. Thus the proteolytic elimination of altered proteins as well as modulation of activity of those remaining leads to dynamic change of proteome composition and function (proteodynamics) in aging lymphocytes.

Henriques et al. presented that there is increasing evidence that a number of potentially informative biomarkers for Alzheimer disease

(AD) can improve the accuracy of diagnosing of this form of dementia, especially when used as a panel of diagnostic assays and interpreted in the context of neuroimaging and clinical data. Moreover, by combining the power of CSF biomarkers with neuroimaging techniques to visualize A β deposits (or neurodegenerative lesions), it might be possible to better identify individuals at greatest risk for developing MCI and converting to AD.

Seo et al. examined in their study the protective effects of Borage officinalis against skin photodamage in UVB-exposed normal human dermal fibroblasts (NHDFs) in vitro and hairless mice in vivo. BO downregulated the expression of MMP-1, MMP-3, and IL-6, and enhanced TGF- β 1 by modulating activator protein (AP-1) and nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signaling in UVB-irradiated NHDFs. Their results demonstrate that BO can be used in functional foods, cosmetic products, and medicines for prevention and treatment of UVB-induced skin photodamage.

Interesting, live and thought-provoking discussions occurred after each presentation as well as after each session. A general discussion was also organised on the future of the bio-gerontological research and its future clinical application.

We sincerely expect that the papers presented here will help to better understand the complexity, the systems biology approach and the role of aging in chronic diseases, as well as future means to influence it for longer and enjoyable healthspan.

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Tamas Fulop*, Anis Larbi¹

Department of Medicine, Geriatric Division, Research Center on Aging,
Université, de Sherbrooke, Qc, Canada
E-mail address: Tamas.Fulop@USherbrooke.ca

* Corresponding author.

¹ A*STAR, SIngN, Singapore, Singapore.