Chapter 4
Geroscience

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Abstract Geroscience is an emerging discipline that examines the relationship between biological mechanisms of aging across different species with the goal of understanding the molecular and cellular pathways underlying age-related diseases. Geroscience is based upon finding connections between the so called "hallmarks of aging", a term that refers to stress adaptation, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, stem cells and regeneration as well as nutrient sensing to elucidate processes damaged in chronic diseases highly prevalent in older people. In this chapter, we tried to explain the origins of Geroscience, its relevance to the study of aging and its connection to disease, as well as to emphasize specific experimental findings that resulted from studies of animal models focused in replicating the physiopathological features of age-related diseases such as neurodegenerative and cardiovascular diseases, sarcopenia and osteoporosis, cancer, diabetes and frailty. Finally, we discussed some potential biomarkers suggested to improve the diagnosis or accelerate the identification of therapeutic targets in order to minimize the negative impact of chronic diseases during aging.

Keywords Geroscience · Biology of aging · Animal models · Age-related diseases

4.1 Introduction

The aging process has been studied from several perspectives including molecular, physiological, geriatric, epidemiological, economic, cultural, psychological and social approaches. Currently, the molecular mechanisms underlying aging have been delineated through the discovery of various molecular pathways such as inflammation, oxidative stress, protein misfolding, cancer progression, hormonal and endocrine disruptors, energy metabolism, cell degeneration and death, neuronal plasticity, neuronal transmission, gut microbiota, etc., in non-vertebrate models, e.g. yeasts, worms and flies as well as in vertebrate models, e.g. zebrafish and mice.

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These studies have contributed significantly to our understanding of the basis of age-related diseases [1].

Traditionally, the normal aging process or its pathophysiological conditions have been explored from a fragmentary and partial point of view. To mitigate this limited approach Dr. Gordon Lithgow and his scientific group from the Buck Institute for Research on Aging, have coined the term Geroscience and advocated the development of an emerging discipline also named Geroscience, as an approach for understanding the processes of normal aging and age-related diseases through an integrative and inclusive point of view encompassing complex interrelationships between the fields of basic and medical science [2]. In this chapter, we will discuss how the so-called hallmarks of aging are fundamentals to accelerate the diagnosis, prognosis and therapeutics of chronic diseases highly prevalent in the aging population.

4.2 Geroscience: The Beginning of a New Discipline

Dr. Felipe Sierra from the National Institute on Aging (NIA) of the United States of America (USA) has been a long-time advocate of the scientific discipline known as Geroscience, and together with other experts have consolidated a "Geroscience Interest Group" (GIG) that already lead to a first international summit meeting held in National Institutes of Health, Maryland on 2013. Among the main goals of this meeting were: (1) to propose a holistic view of aging to address age-related diseases as a group; (2) to share new findings in the field of the biology of aging and assess their impact on a single or several age-related diseases; (3) to find connections between basic areas of the research such as adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, stem cells and regeneration, also known collectively as "hallmarks of aging"; (4) to recognize the most important dietary, genetic and pharmacological interventions in animals models and their contribution to lifespan and healthspan; (5) to develop new animals models of aging and, finally (6) promote comparative studies to detect new susceptibility factors for chronic diseases [3]. A consensus in the scientific community recognizes aging as an important risk factor for the development of chronic diseases. Following this premise, the GIG of the NIA organized a second Geroscience summit in order to discuss how three specific diseases -cancer, HIV/AIDS and diabetes mellitus (DM)- are driving aging, a new idea called "Reverse Geroscience". The main goal of this meeting was to explain whether or not chronic diseases are impacting the cellular mechanisms grouped as hallmarks of aging in a transitory or permanent manner [4].

4.3 Advances in Geroscience: Therapies and Interventions

The main contribution of Geroscience to the study of aging has been to take advantage of the knowledge generated by a multidisciplinary approach. Examples of subjects widely explored by this discipline are: (1) cancer progression.- the time-dependent accumulation of cellular damage as well as prolonged exposure to carcinogens or genotoxic agents increase the abnormal expression and activity of proteins involved in the control of the cell growth and proliferation, modifying cellular senescence and programmed cell death producing the progression of tumors [5]; (2) cardiovascular disease.- the surge of macromolecular damage and the increase in the generation of reactive oxygen species by mitochondria in cardiac cells release an large number of molecular factors that give rise to vascular inflammation, cell senescence, apoptosis, decrease of cell renewal, altered proteostasis, reduction of angiogenesis, adverse extracellular matrix remodeling, impaired nitric oxide metabolism with endothelial dysfunction, etc., affecting the correct function of the heart and vascular system [6]; (3) neurodegenerative diseases.- Alzheimer's disease (AD) and Parkinson's disease (PD) have been the most studied neurodegenerative diseases worldwide and highly associated with aging. Animals models have been relevant to understand some pathophysiological features observed in AD or PD [7, 8]; (4) sarcopenia and osteoporosis.- the older adults suffer skeletal and muscle disorders causing disability and loss of movement significantly affecting their daily activities. Aging alters bone formation, accelerates bone resorption, enhances sympathetic tone, changes the parathyroid/vitamin D axis, impairs renal function, increases the loss of muscle mass and reduces muscle strength, etc., all these changes could be explained by the presence of critical molecular determinants during aging: excess mitochondrial autophagy, metabolic dysfunction, accumulation of reactive oxygen species and cell senescence in the stem cell pool [9, 10]; (5) DM.- several epidemiological studies have suggested that DM has a role in the development of dementia. However, the factors linking DM with AD are largely unclear. Some of the risk factors proposed to play a role in the neurodegenerative process and the progression of the dementia of AD are: hyperglycemia, insulin resistance, oxidative stress, activation of inflammatory citokines and damage to the micro/macrovascular system; all these factors have also been observed in patients with DM [11, 12]; and (6) frailty.- this condition produces changes in the adaptive mechanisms that promote resilience and significantly reduces homeostatic capabilities while increasing sensitivity to stress; in consequence a critical number of signs and symptoms converge in the same people, these include: muscle weakness, slowness, low physical activity, weight loss and exhaustion –according the frailty phenotype. The biological systems most affected by this condition are: endocrine, inflammatory, muscle-bone, central and peripheral nervous and immune **[**13**].**

4.4 Biomarkers of Aging and Age-Related Diseases

Nine molecular biomarkers, known as "hallmarks of aging", have been identified, categorized and related to the aging process, and these are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, lack of nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cells exhaustion and altered intercellular communication (please refer to chapter 3-Biomedical research in aging; for a complete description of the hallmarks of aging). These biomarkers could help to understand the variables that accelerate, delay or diminish the aging process [14]. In the following sections, we will briefly describe main biomarkers identified and proposed for discerning some chronic diseases associated to aging.

4.4.1 Biomarkers for Neurodegenerative Diseases

Biomarkers suggested for AD are the loss of proteostasis and protein misfolding mainly observed in the beta-amyloid peptides and amyloid precursor protein producing amyloid plaques [15] or by an abnormal hyperphosphorylation of tau protein inducing the formation of neurofibrillar tangles in specific brain areas [16]. Double Strand *DNA* Breaks (DSB) is another interesting biomarker for AD, because in human brains of patients with AD a high content of DSB has been observed in comparison with normal patients [17]. On the other side, dysfunctional synaptic transmission is a way to evaluate cellular communication; consequently, the detection of neurogranin, a neuronal protein which participates in synaptic signaling through the regulation of calmodulin availability, could be one of the most interesting and newer promising biomarker for the diagnostic and prognosis of AD [18]. PD is characterized for the loss of dopaminergic neurons in brain areas called basal ganglia and substantia nigra, in addition to the presence of Lewy bodies, which are composed by abnormal deposits of a protein called alpha-synuclein. This protein has been proposed as a main biomarker in PD [19]. Other proteins proposed as biomarkers of PD are Parkin, DJ-1 and LRKK2, which are involved in the maintenance of membrane potential of the mitochondria. Any modification or changes in their molecular functions alters ATP synthesis and produces an aberrant assembly of complexes in the mitochondria thus generating a deficient cellular communication in neurons of the brain areas affected by PD [20, 21].

4.4.2 Biomarkers for Muscle Disorders

Sarcopenia is characterized by a significant decrease in muscle mass and strength, as well as slow physical performance [22]. One of the biomarkers more studied in sarcopenia is myosin heavy chain protein, a protein involved in myogenesis [23].

The maintenance of muscle mass depends on the balance between apoptosis and the mechanisms of regeneration. Thus, some biomarkers proposed to assess apoptosis are caspase 3, apoptosis-inducing factor, Apaf1, Bax and DSB proteins [24]; while proteins for detecting muscular regeneration as Pax7 and Pax3 or for identifying early or late myogenesis as MyoD or Myf5 have been proposed to detect the loss of muscle mass [25]. On the other side, muscle satellite cells (SC) are stem cells specifically localized between basal lamina and sarcolemma of myofibrils, SC participate in the regeneration of muscle in response to injury and their number decreases with aging. For these reasons SC are being considered as a biomarker to detect sarcopenia [26]. Finally, mitochondrial dysfunction is a determinant factor in the physiopathological events of sarcopenia because the mitochondria contribute significantly to energy production for muscle function. The biomarkers identified in the mitochondrial dynamics include fusion (Mitofusins: Mfn1 and Mfn2 and OPA1), fission (Fis1, Mff y Drp1*) and* biogenesis (PGC-1α) proteins; all of which are affected in sarcopenia [27].

4.4.3 Biomarkers for Bone Diseases

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. This disease is very common in older adults and is the main cause of bone fracture. Recently, biomarkers for bone have been classified into two categories: (1) bone formation and (2) bone reabsorption. The first group includes bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide and procollagen I carboxyterminal propeptide [28]. In the second group, we have: pyridinoline, deoxypyridinoline, C-telopeptide, N-terminal telopeptide and tartrate-resistant acid phosphatase [29]. A newer biomarker proposed to study bone formation is sclerostin, a protein produced by the osteocytes. High levels of sclerostin have been detected in patients with high bone mineral density suggesting that this protein could be an excellent biomarker for mature osteocytes [30].

4.5 Perspectives

For a decade, Geroscience has been a fashionable interdisciplinary field with a positive reception and growing acceptance within the international scientific community that concentrates all possible efforts from different disciplines to reduce the negative impact, disability and progression of the chronic diseases during all the stages of aging. Since the birth of Geroscience, biomedical specialists have engaged in the study of aging, focusing their attempts to advance knowledge in order to help people affected by chronic diseases. The popularity of Geroscience in the gerontological and geriatrics world has encouraged the establishment of international scientific networks such as the Geroscience Network, integrated by 18 institutions from

United States of America [31]. This network includes basic scientists, clinicians, and other health professionals with the goal of exchanging ideas in different workshops focused on the mechanisms underlying of the aging process. Another example is the Geroscience Center for Brain Health and Metabolism (GERO) recently created in Chile, where scientists from different disciplines are doing fundamental research in close association with clinical fields from neuroscience, molecular biology and genetics to develop interventions to slow aging and counteract age-related diseases. Lastly, since 2010, Mexico created a national network on aging, health and social development to connect scientists interested in the study of the aging from different disciplines such as basic science, clinical practice, epidemiological and social to integrate and consolidate their advances in favor of the aging people. In addition, an international scientific meeting focused on Geroscience was held in Mexico City on October 2016, with the goal of emphasizing for the value of studying aging from an integrative point of view.

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