Biological Links between Aging and Frailty

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The life expectancy of the global population has increased. Aging is a natural physiological process that poses major challenges in an increasingly long-lived and frail population. Several molecular mechanisms are involved in aging.

Keywords: aging ; Mediterranean diet ; molecular pathways

1. Introduction

Currently, the global population has a notably increased life expectancy compared to decades ago, exceeding 60 years of age in most cases. According to the World Health Organization (WHO), the percentage of people over 60 years of age will double globally by 2050 [1]. However, a longer life expectancy leads us to reconsider not only the health of older people but also what kind of implications aging has [2].

Aging is a natural physiological process that leads to a progressive loss of cellular functionality, with consequences that predispose people to an increased risk of frailty, morbidity, and mortality [3]. The role of lifestyle and diet can promote “healthy aging”, in which quality of life takes precedence. According to the WHO, this concept refers to the process of developing and maintaining a functional capacity that enables well-being in old age [1][4].

Several cellular and molecular hallmarks are involved in the aging process. In particular, there are nine hallmarks that are decisive in the aging process: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, the dysregulation of nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell depletion, and altered intercellular communication [5]. These molecular mechanisms are involved in the development of age-related diseases such as cancer, obesity, diabetes, cardiovascular disease (CVD), and neurodegenerative diseases [3]. These age-related diseases have been associated with risk factors that can be modified mainly through nutrition, which constitutes one of the pillars of health [6]. In addition, the microbiota, which is modified by diet, has also been involved in aging [6]. It has been suggested that the age-related decline in immune system function (immunosenescence) and chronic low-grade inflammation could lead to microbiota disturbances that are associated with several age-related pathologies. Thus, it has been argued that a balanced diet can modulate the proliferation of specific bacteria within the gut microbiota. This has been associated with improved health status in older people [7].

There is an increasingly aging global population. However, the way to achieve healthy aging has not yet been fully elucidated. The loss of function and frailty syndrome associated with aging increases the vulnerability of the elderly and their propensity to disease. There are different molecular pathways or hallmarks involved in aging that bring us closer to understanding the deterioration associated with the senescence process, such as genomic instability, telomere attrition, epigenetic effects, proteostasis, nutrient-sensing pathways, mitochondrial dysfunction, cellular senescence, stem cell depletion, and altered intercellular communication. Likewise, microbiota disturbances seem to play a relevant role in frailty in the elderly.

It has been shown that MedDiet promotes healthy aging, increasing the life expectancy of the population. These contents have shown that MedDiet positively influences the molecular pathways that determine age. Consequently, MedDiet has been associated with a lower risk of age-related diseases, mainly CVD, neurodegenerative, and oncological diseases. Therefore, further evidence of the beneficial effects of this dietary pattern on human health and longevity has been provided. However, most studies do not evaluate the impact of the Mediterranean diet pattern as a whole on the hallmarks of aging but rather its individual components, especially certain bioactive components. Certainly, there are some clinical trials exploring the role of the Mediterranean diet (mostly PREDIMED substudies), but they focus on specific dietary supplementation with nuts or EVOO (especially virgin (VOO) and extra virgin (EVOO)). Therefore, it would be useful to evaluate the pattern as a whole without special emphasis on these more studied components. In addition, more quality

studies on the MedDiet and the prevention of frailty and disease in aging are needed, as many studies are observational, and causality cannot be determined.

2. Aging and Frailty: Biological Links

From a biological point of view, aging can be defined as the physiological and progressive accumulation of senescent cells in organs and tissues, which occurs during the lifetime of an individual and leads to progressive functional slowing or the total loss of function [8][9][10].

Pleiotropic antagonist genes comprise a set of genes that regulate cellular senescence, performing an important role in preventing the degeneration of malignant cells in the cell cycle [11][12]. These genes are also involved in protective mechanisms in physiological cellular senescence processes and in age-related diseases. However, aging cells produce proinflammatory and lytic extracellular matrix molecules in a process known as the senescence-associated complex secretory phenotype (SASP), resulting in degeneration and pathological senescence. Moreover, the aging process involves the immune system; in particular, the cell-mediated defense mechanism is slowed down. Senescent cells do not produce sufficient signals to activate immune cells. Likewise, senescence is induced by the accumulation of various factors at the cellular level that is responsible for macromolecular damage, such as secondary DNA alterations due to oxidative damage, telomere shortening, and endoplasmic reticulum (ER) degeneration [13]. Thus, aging is the result of multifactorial interactions between local and systemic environmental factors and involutional factors due to cellular senescence. Therefore, the number of senescent cells in a person's body increases with age as the aging immune system becomes less efficient and senescent cells accumulate. This makes individuals more vulnerable to further deterioration after exposure to environmental stressors [13]. The disease occurs when environmental stressors attack tissues that are already in the presence of senescent cells with very low resilience [14][15].

Frailty develops due to an increasing decline usually linked to age, severe deterioration, and the onset of pathological states. This leads to a condition of increased vulnerability and reduced adaptive capacity, and ultimately, negative health changes are triggered by even mild stressors. It is considered more appropriate to speak of "frailty syndrome": a chronic pathological condition resulting from the interaction between several factors, including aging-related physiological alterations, pluripathology, nutritional deficiencies up to severe malnutrition, and the negative impact of socio-environmental factors [16]. In fact, a high proportion of undernourished people are frail, and undernutrition leads to weight loss, which can contribute to frailty syndrome [17]. At the other extreme, obesity increases the risk of frailty [18]. In terms of body composition, frailty has been associated with a higher body fat mass and fat percentage and with a low muscle mass and is often without association with the body mass index [19][20][21].

All of this can lead to the frail elderly losing all self-sufficiency, increasing the risk of falls, and can result in a state of confusion with severe impairment of cognitive functions that ultimately increases the risk of the development of diseases [22].

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