Aging-Related Processes that Promote Atherogenesis: Il-6 as a Possible Shared Pathway

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ARTICLE INFO

Citation: José Antonio Reyes Pinto, Dina Rafaela González Hernández, Ricardo Antonio Rendon Muñoz, Adrian de Jesus Gorrostola Muñoz, Carlos Andrés Genes Vasquez, Silvia Juliana Rodríguez Pérez. Aging-Related Processes that Promote Atherogenesis: Il-6 as a Possible Shared Pathway. Biomed J Sci & Tech Res 42(3)-2022. BJSTR. MS.ID.006763.

ABSTRACT

During aging, IL-6 signaling in bone marrow adipocytes increases. it may also have proatherogenic effects directly on the vasculature. Aging is associated with increased IL-6 levels, possibly mediated by increased vascular smooth muscle cell (VSMC) production, mitochondrial genomic instability, and decreased mitochondrial function in the vasculature.

Summary

During aging, IL-6 signaling increases in bone marrow adipocytes. it can also have pro- atherogenic effects directly on the vasculature. Aging is associated with increased IL-6 levels, possibly mediated by increased production of vascular smooth muscle cells (VSMCs), mitochondrial genomic instability, and decreased mitochondrial function in the vasculature.

Keywords: Aging; Atherogenesis; Interleukin 6

Abbreviations: VSMCs: Vascular Smooth Muscle Cells; CVA: Cerebrovascular Accident; TIA: Transient Ischemic Attack; CRP: C-Reactive Protein; TNF: Tumor Necrosis Factor

Introduction

Aging is a biological process that occurs at the cellular, molecular, and genetic level associated with a deterioration of the physiological and reproductive functions necessary for our survival with the passage of time [1].

The Natural Aging

process is characterized by being universal since it must occur in all individuals of a species, irreversible since all human beings have a limited survival, progressive since it is a process and not a sudden phenomenon, and finally, degenerative since it implies a loss of bioenergetic capacity and functional performance of living beings [2]. Multiple mechanisms are involved in the aging process, including epigenetic factors, DNA damage, mitochondrial dysfunction and telomeric shortening [3]. At the cellular level, there is an imbalance between the increase in oxidative stress and the capacity of its protective response to such damage, contributing to cellular senescence, in which cells stop proliferating and become dysfunctional. Consequently, reactive oxygen species (ROS)

accumulate, inducing an increase in the secretion of inflammatory molecules that affect the cell itself and the surrounding tissue. The response of our organism to the induced damage is to generate a process of chronic inflammation [3]. For all these reasons, the aging process could be understood as an accumulation of senescent cells in aged tissues and organs. In today's society, chronological aging is associated with the development of age-related diseases, such as heart failure, diabetes or arteriosclerosis, and several studies have shown that the accumulation of senescent cells plays a causal role in these pathologies [4]., resulting in a deterioration in the quality of life by limiting the normal activities of patients. It is becoming increasingly important not only to prolong longevity, but also to make it as healthy as possible, making it possible to evaluate the number of years lived, the quality of life and the absence of disability during those years [5].

Materials and Methods

We performed a detailed bibliographic search of information published since 2017, in the databases pubmed, Elsevier, scielo,Update, medline, national and international libraries. We used the following descriptors: aging, atherogenesis, interleukin 6. The data obtained ranged from 5 to 15 records after using the different keywords. The search for articles was performed in Spanish and English, was limited by year of publication, and used studies published since 2017.

Result

Research into the mechanisms involved in the aging process has increased in recent years. These advances have made it possible to identify therapeutic targets to improve health in this phase of life, while minimizing side effects [1]. A review on aging markers attempts to identify and classify the cellular and molecular characteristics of aging, proposing nine signals whose modulation would accelerate or delay the normal senescence process. These are: genomic instability, telomeric shortening, epigenetic alterations, loss of proteostasis, nutrient dysregulation, mitochondrial dysfunction, cellular senescence, stem cell depletion and altered intercellular communication [2]. In recent years, different studies have been carried out to help explain the genetics of human longevity, identifying polymorphisms in genes encoding proteins that influence certain pathways of a model organism and affect life expectancy. These genes can participate in the different processes that determine aging, such as: resistance to oxidative stress, DNA repair, mitochondrial function, telomere shortening, and cell cycle control, among others [3,4,6]. Previous studies have also demonstrated the association between LTL shortening and atherosclerosis. In a prospective study involving 768 participants in the PLIC study, volunteers in whom the progression of carotid lesions is assessed by determining the intima-media thickness

of the common carotid artery and relating it to LTL, at baseline and at 6 years, showed an inverse relationship between the two, independently of classical cardiovascular risk factors [5,7].In the longitudinal InCHIANTI study, with more than a thousand participants, aged over 60 years, followed for 9 years, an increase in morbidity was observed in older patients with high levels of IL-6 [8].The relationship observed has led to the concept of "inflammatory aging", defined as a situation in which an elevation of inflammatory biomarkers (CRP, interleukins, TNF- a) occurs and favors the development of chronic pathologies [9].

Longitudinal studies show that elevated levels of inflammatory markers such as IL-6, TNF-a or CRP are independent risk predictors of cardiovascular disease in young adults and older population [10]. Currently, the GenAge database provides more than 300 aging-related genes and LongevityMap contains more than 500 entries indicating genes, loci, and variants studied in the context of human longevity and healthy aging [11,12]. Recent studies have associated the chronic inflammatory processes of natural aging as a risk factor or pathogenic mechanism of cardiovascular disease. Longitudinal studies show that elevated levels of inflammatory markers such as IL-6, TNF-a or CRP are independent risk predictors of cardiovascular disease in young adults and the elderly population [13,14]. Currently, multiple models have been developed and published to evaluate patients and predict the risk of developing cardiovascular disease, allowing patients to be classified into different levels and to modify management and therapeutic strategies according to the calculated risk. The best known is the Framingham score, which allows us to determine the risk of developing coronary heart disease in 10 years; it is a multivariate risk prediction algorithm that includes the following factors for the calculation: age, gender, tobacco use, TC, LDL-C, LDL-C, HDL-C, TAS and diabetes mellitus, although some authors believe that this score overestimates the risk of coronary heart disease in European populations. For this reason, the European Society of Cardiology and The Second Joint Task Force developed a risk classification system using data from 12 European countries, forming the SCORE project [15].

Discussion

Atherosclerosis is a chronic, generalized, and progressive disease that mainly affects medium- sized arteries. Clinically it manifests as ischemic heart disease, cerebrovascular disease, or peripheral arterial disease. The risk factors for developing it are the same for the different vascular territories, and the presence of atherosclerosis in each vascular territory is often associated with the involvement of other territories and the progression of aging [16]. Coronary artery disease is a chronic inflammatory process characterized by thickening of the intima and media arterial layers of the vessels with loss of their elasticity. When this process affects the coronary arteries, it can manifest as

stable angina, acute coronary syndrome, myocardial infarction, or sudden death. When it affects the brain, it presents as an acute cerebrovascular accident (CVA) or a transient ischemic attack (TIA) [17]. Aging is associated with the development of a chronic low-grade proinflammatory state, characterized by an increase in inflammatory markers in cells and tissues, becoming a key factor for the onset of multiple age-related chronic diseases, including cardiovascular disease, cancer (84), kidney disease, dementia, or depression, and favoring disability in daily activities, frailty, and premature death [18-23]. The proinflammatory state is defined by elevated levels of certain markers such as IL-1, IL-6,IL-8, C-reactive protein (CRP), IFN-a, IFN-b, tumor necrosis factor (TNF), its soluble receptors (TNF receptors 1A and 1B) and serum amyloid A. For this reason, inflammation is considered a marker of accelerated aging and is considered one of the pillars of the biology of aging [24]. Inflammation has been evolutionarily selected as a defensive mechanism in infections, preventing cancer and repairing damaged tissues. When inflammation becomes a chronic process (In advanced ages of aging), cardiovascular, renal, neurological, and other pathologies appear [25].

Among the proinflammatory cytokines, IL-6 is notably implicated in age-associated vascular disease, and its higher levels are correlated with greater disability and mortality in the elderly [26].CRP levels are associated with increased arterial stiffness in the elderly [27] and monocyte chemotactic protein 1 (MCP-1) has a higher expression in the thickened arterial intima of vessels in older adults compared with younger people [28]. By increasing IL-6 signaling in bone marrow adipocytes, it may also have proatherogenic effects directly on the vasculature. Aging is associated with increased IL-6 levels, possibly mediated by increased vascular smooth muscle cell (VSMC) production, mitochondrial genomic instability, and decreased mitochondrial function in the vasculature. Reduced mitochondrial function alters mitophagy and increases IL-6 levels, creating a positive feedback loop that accelerates atherogenesis. Vascular aging also leads to the production of chemoattractant that increase myeloid cell recruitment to the arterial wall, further promoting atherosclerosis.

Conclusion

Despite the existence of many studies that evidence key components in the aging process, there are still studies that clarify the relationship between aging and the development of many pathologies at the anatomical level, especially those that represent a cardiovascular and neurological risk. It is important to highlight that up to now the timely prevention of risk factors that favor the early development of aging is still important as a common factor, healthy eating, exercise and the consumption of supplements with certain synthetic compounds that have antioxidant or anti-inflammatory effects could be considered as beneficial to prevent or

reverse dysfunction in aging. However, studies suggest that healthy dietary habits involving increased intake of natural antioxidants or boosting endogenous antioxidants would be more beneficial for vascular pathology, as antioxidant status is more effective than exogenous antioxidant addiction. These measures include the adoption of a Mediterranean diet, supplemented with olive oil and nuts, which reduces the incidence of cardiovascular disease.

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