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Letters to the Editor / Cartas al Editor

WHY DO WE AGE? THEORIES AND PRACTICAL CONSEQUENCES

José-Miguel López-Novoa

Professor of Human Physiology. Department of Physiology and Pharmacology Faculty of Medicine. University of Salamanca. Spain

Email: jmlnovoa @ gmail.com

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Señor Editor:

Aging is the process of becoming older. This is an obvious definition, but precisely defining what is aging in the living being is rather problematic, and each expert in the field will have their own version. It is believed that aging is the consequence of two associated, but not identical processes: the attenuation in function and the reduction in adaptive capacity. The fundamental characteristic of the physiological ageing process is the attenuation of functional performance. However the rate of functional capacity varies within individuals and with the type of function assessed. This reduced functional performance, leads to older people taking longer, or sometimes being unable to adapt to biological, physical, psychological, environmental or social situations of overload or restriction.

Aging is a complex phenomenon, where damage accumulation, increasing deregulation of biological pathways, and loss of cellular homeostasis lead to the decline of living being functions over time. Aging should be radically differentiated of "age-associated diseases" e.g. those diseases whose prevalence increases dramatically with age. The major difference is that these diseases do not affect to all the subjects without exception. For instance, increase arterial stiffness is a characteristic of ageing in the vascular system, but atherosclerosis is not.

There is no single mechanism which may explain aging; it is multi-factorial, multiform, and asynchronous. Aging is modulated by hereditary, environmental, dietary and healthcare factors. Aging occurs in all the organs and systems of the body, however not all organs age uniformly. There are some functions which are relatively well conserved until old age, whilst others decline in function much sooner, but this asynchrony is specific for each individual.

Three groups of theories have been proposed to explain the ageing phenomenon:

environmental, genetic and mixed theories[1].

The environmental or exogenous hypothesis suggest that age is modulated by multiple factors from the environment, diet or derivatives of metabolism, exert a series of injuries on macromolecules, cells and tissues, but do not directly affect DNA nucleotides sequence, but it can modify secondary DNA structure.

The genetic theory proposes that ageing is due to a predetermined genotype that specifies the appearance of phenotypic changes associated with age, and thus, the velocity of ageing is genetically pre-programmed at birth. Some scientists agree that ageing is coded within the DNA of each cell, whereas others believe that ageing is encoded in the systems that regulate and control the entire organism, i.e. the endocrine, nervous and immune systems. It appears that the changes observed in the nervous, immune and endocrine systems are more a consequence than cause of ageing. However ageing is not pre-programmed by specific genes, i.e. there are no "gerontogens" which have the specific evolutionary function to cause aging.

The mixed theory of aging proposes that genes and environment interact to induce aging. Thus, aging is neither an entirely stochastic process nor an exclusively gene background-dependent process, but it is subject to extensive regulation by an elaborated signalling network. This network can integrate a variety of aging-regulatory stimuli, i.e. fertility, nutrient availability, or diverse stresses, and relay them via signalling cascades into gene regulatory events - mostly of genes that confer stress resistance and thus help protect from damage accumulation and homeostasis loss. Therefore, each organism has a certain genetic predisposition to ageing, which can be modulated by the action of exogenous agents or products of its own metabolism. This theory conciliates both the genetic and environmental theories of ageing.

Major exogenous factors involved in aging: nutritional factors are among the most important exogenous influences on living organisms aging. The most important evidence in this field is that reduction in calorific intake has the capacity to increase life expectancy and diminish the symptoms of ageing in many laboratory animals including the fruit fly Drosophylla melanogaster, the nematode Caenorabditis elegans, in rodents such as rats and mice, and even in primates. The restriction of calories not only increases survival and maintenance of a youthful appearance, but it also helps to maintain basic aspects of structure and function.

Metabolic factors: It has been proposed that accumulation of metabolic waste products damaged macromolecules produced by the chemical reactions, such as end products of advanced glycosylation could be a factor contributing to cellular ageing. Oxidative stress resulting from changes in the oxidant-antioxidant balance seems to play a major role in this phenomenon. Reactive Oxygen Species (ROS) damage macromolecules within cells, and this damage is minimized by the action of antioxidants. This key observation could also explain the inverse relationship between levels of antioxidants and longevity: the animals with longest life spans have lower levels of antioxidants simply because their rate of ROS production is lower[2]. However there are also many evidences demonstrating that aging can be also related to the ability of the organism to remove the damaged molecules from the cells[3].

Major genetic factors involved in aging, programmed ageing: the proponents of the idea that duration of life and the rate of decrease in biological activity is actively programmed

in the genome, base their theory on examples of ageing and cellular programmed death. However, There are no genes with the specific evolutionary function of causing aging Among the possible mechanisms involved are the genetic regulation of metabolic control, that would influence the oxidant/antioxidant balance or the ability of the organism to remove the damaged molecules from the cells.

Telomere shortening: Telomeres are complexes of proteins and nucleic acids that are found at the end of chromosomes, protecting them against degradation and thereby allowing replication of the genome without the loss of terminal coding sequences. In each mitotic division, telomeres shorten, and this shortening is restored in the germinal or stem cells by the enzyme telomerase, which is absent in somatic cells and tissues. Consequently, in these tissues, the telomeres shorten with each cell division. Thus, after a finite number of cell divisions, the telomeres can no longer fulfil their protective role, leading to impaired chromosome replication. Many studies have demonstrated a lose relationship between telomeres length and aging[4].

The error-catastrophe theory of aging proposed by Orgel in 1963[5], states that aging is the result of the accumulation of errors in cellular molecules that are essential for cellular function and reproduction that eventually reaches a catastrophic level that is incompatible with cellular survival. In brief, the theory is based in the following points:
a) The transfer of information from DNA to RNA (transcription) and from RNA to proteins (translation) does not always occur with absolute fidelity, thus producing abnormal proteins.
b) Proteins also participate in both information transfer process.
c) A very small proportion of altered proteins implicated in transcription or translation would induce a continuous progressively higher production of malfunctioning proteins.
d) When it is exceeded the cellular capacity to repair or eliminate abnormal proteins or oligonucleotides, would lead to a massive cellular metabolic alteration (catastrophe).

This theory predicts, therefore, an abnormal protein accumulation in aged cells - which is true, as above explained. However, it most of the alterations observed in these abnormal proteins are not due to errors in translation but to posttranslational modifications, such as non-enzymatic glycosylation, free radicals and other causes previously mentioned. Currently it is believed that a constant and low error rate can be maintained indefinitely, not inevitably producing a cellular catastrophe[6].

Epigenetic changes: aA growing body of work has recently underscored the importance of the epigenetic changes during aging, where it not only undergoes drastic age-dependent changes but also actively influences the aging process. The term epigenetic refers to functionally relevant, heritable changes to the genome that do not involve a change in the nucleotide sequence. Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence. Recent studies have investigated aging-related DNA methylation as a biomarker that predicts cellular age. Growing evidence proposes that nutrients play a crucial role in the regulation of epigenetic modifiers. Because various nutrients and their metabolites function as substrates or cofactors for epigenetic modifiers, nutrition can modulate or reverse epigenetic changes in the genome as well as expression patterns. Thus epigenetic changes could explain the interaction between the genetic and environmental mechanisms of ageing[7].

Transcription factors are proteins that, synthesized in the citosol, enters to the nucleus and control the rate of transcription of genetic information from DNA to messenger RNA. Transcription factors contain at least one DNA-binding domain, which attaches to a specific sequence of DNA adjacent to the genes that they regulate, the so-called gene promoters. The function of transcription factors is to regulate-turn on and off-genes in order to make sure that they are expressed at the right time and in the right amount throughout the life of the cell and the organism, according to their metabolic changes or requirements. A growing body of work has recently underscored the importance of the epigenetic changes during aging[8].

Chromatin structural changes: Chromatin is a complex of macromolecules found only in eukaryotic cells, consisting of DNA, protein, and RNA. The primary functions of chromatin include, among others, to wrap up DNA into a more compact nature, to prevent DNA damage, and to control gene expression and DNA replication. The primary protein components of chromatin are histones that compact the DNA. It has been recently reported that significant chromatin structural changes occur during physiological aging and senescence. These alterations range from alterations in the nuclear envelope and the structure of chromosome territories within the nucleus to changes in nucleosome positioning and histone modifications[4]. How chromatin organization influences aging and is altered by it and the related process of cellular senescence is only beginning to be explored.

Practical ideas based on the concept of aging: although all age-related diseases are more frequent in aged individuals, aging in itself cannot be considered a disease. If aging is considered as a disease, in an ideal condition a disease-free state could be achieved during all the life. However, if aging is not considered as a disease, our approach towards aging interventions should be converted from the so-called anti-aging treatments to achieving healthy aging. But what is healthy aging? Health is often described either as the absence of diseases or as a vague concept of well-being, without having any objective measurements for that concept[9].

There is no doubt that almost all the organs or systems changes more or less their function during aging, but the symptoms of these changes should not be confounded with symptoms of a disease, and thus, the individual should not be treated as having a disease, as they can be subjected from pharmacological treatments inadequate for his/her aging or deprived of a treatment for suspecting some organ damage. As an example we will shortly develop the case of overdiagnosis of chronic kidney disease (CKD) in the aging.

The gold standard for the diagnostic of renal failure is to measure the Glomerular Filtration Rate (GFR) which is usually achieved by measuring the renal creatinine clearance. As the clearances studies require urine collection for some period of time, which is a tedious and sometimes unavailable procedure, a number of formulae to estimates GFR (eGFR) from blood creatinine levels have emerged (10). The use of some of these formulae may induce to undesirable/serious consequences for the healthy aged, that includes:
a) Use for eGFR estimation formulae not validated for persons aged >70 years.
b) To set the boundary between renal health and renal disease in the critical value of eGFR < 60 ml/min/m2 regardless of age, neglecting the well-established decrease of GFR according to age[11].

c) The increased sensitivity of the tests to discover early CKD has been enhanced at expenses of specificity, thus many healthy subjects are wrongly classified as having a CKD by eGFR calculation.

The inobservance of the above considerations may lead to the adverse situation that aged persons with a GFR normal for his age, may be classified as suffering from CKD As a result, apart for the exclusion in clinical trials, may be deprived from medical treatments or surgical procedures in whom the prospect of the medicament or the guidelines contra-indicate the treatment in cases of CKD[12].

REFERENCES

1. da Costa JP, Vitorino R, Silva GM, Vogel C, Duarte AC, Rocha-Santos T. A synopsis on aging-Theories, mechanisms and future prospects. Ageing Res Rev. 2016;29:90-112.

2. Barja G, Herrero A Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. FASEB J 2000;14:312-318.

3. Chandrasekaran A, Idelchik MDPS, Melendez JA. Redox control of senescence and age-related disease. Redox Biol. 2017;11:91-102.

4. López-Otín C., Blasco M.A., Partridge L., Serrano M., Kroemer G. The hallmarks of aging. Cell. 2013;153:1194-1217.

5. Orgel LE The maintenance of the accuracy of protein synthesis and its relevance to ageing. Proc Natl Acad Sci United States 1963;49:517-521.

6. Milholland B, Suh Y, Vijg J. Mutation and catastrophe in the aging genome. Exp Gerontol. 2017 Aug;94:34-40.

7. Park JH, Yoo Y, Park YJ. Epigenetics: Linking Nutrition to Molecular Mechanisms in Aging. Prev Nutr Food Sci. 2017 Jun; 22(2): 81-89.

8. Zhou X, Sen I, Lin XX, Riedel CG. Regulation of Age-related Decline by Transcription Factors and Their Crosstalk with the Epigenome. Curr Genomics. 2018;19:464-482.

9. Rattan SI. Aging is not a disease: implications for intervention. Aging Dis. 2014;5:196-202.

10. Musso CG, Álvarez-Gregori J, Jauregui et al Glomerular filtration rate equations: a comprehensive review. Int Urol. Nephrol. 2016; 48:1105-10.

11. Fehrman-Ekholm I, Skepoholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. Scand J Urol Nephrol) 2004;38(1):73-7.

12. Alvarez Gregori J.A., R.N., Mena C., Ardanuy R., Jauregui R. Macias-Nuñez

JF. The value of a formula including haematocrit, blood urea and gender (HUGE) as a screening test for chronic renal insufficiency. The Journal of Nutrition, Health & Aging, 2011; 15:480-484

CORRESPONDENCE:
José Miguel López-Novoa
Professor of Human Physiology
Department of Physiology and Pharmacology
Faculty of Medicine
University of Salamanca
Spain Corresponding author:
Email: jmlnovoa @ gmail.com