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Why do we Age?

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Abstract

Several theories have been proposed to explain why we age. In general the same cause has been considered for all organisms although aging is not identical in the different organisms. Some theories suggested a single cause that would trigger a cascade of events leading to the extinction of the organism. Other theories suggested the depletion of a potential, a programmed type evolution, genes differentially expressed through natural selection, or wear and tear through an accumulation of deleterious molecules. There is a discussion going on concerning if there is an insurmountable barrier to the human life span or if it is possible to overcome the actual limit. I think that to find the cause of aging one has to consider the first step for survival in the biosphere - the capacity to meet the energy requirements. Life is dependent on the utilization and transduction of energy and thus has to follow thermodynamic rules. The second law of thermodynamics states that all systems spontaneously change in such a way as to decrease their capacity for subsequent change. A system driven by the utilization of energy, which is in a permanent restructuring has to follow the second law with entropy increasing accordingly.

Keywords: *stress, genes, asymmetric cell division, molecular conformation, thermodynamics.*

Introduction

The question of why we age has been an essential one that human beings have asked for immemorial times. It is still a dream to overcome that barrier and there have been several attempts to achieve it. At least in the industrialized countries the wish has been partially fulfilled. Indeed the increase in the number of survivors has increased spectacularly during the last hundred years, it was larger than during the previous 5000 years; the improvement continues with an increasing number of individuals reaching the present maximal human life span.

The hypothetical limit of the human life span is now discussed among gerontologists. The Bible has the following paragraph expressed in approximately these terms: "The sons of Elohim united with the daughters born from the glebe. Adonai says: my breath will not last in those born from that union. They are flesh, their days will not last more than 120 years". It is amazing, that seems to be approximately the maximal human life span. Whether this limit can be manipulated is now a question open for debate.

Aging is a progressive phenomenon that advances at different rates among the human organs. The follicles in the ovaries start reducing from birth on; the thymus regresses from the time of adolescence; if one learns a language after adolescence inevitably one will speak it with an accent; the weight of the brain decreases after 20 years of age; most professionals in sports have to retire around 30 years of age; the most notorious decline is that of reproductive activity which starts on average between 45 to 50 years. It is then that one can speak of senescence.

Some gerontologists think that senescence is a kind of pathological process that can be avoided. We believe that aging is unavoidable, it is inherent to living beings; living means continuous adaptation through change away from equilibrium, a steady state does not exist in living organisms. The second law states that all systems spontaneously change in such a way as to decrease their capacity for subsequent change. Living organisms are continuously reorganized hence tend to a limit,

Physiological and Pathological Aging

I think that one should distinguish between physiological and pathological aging. There are studies at the cellular level that are representative of the need to make this distinction.

Human mitotic cells have a finite proliferation potential, which was revealed following their serial divisions in vitro where they go through different phases leading to a final post-mitotic stage (Hayflick and Moorhead 1961). Under normal circumstances in vivo the cell division potential declines but is not exhausted.The use of a wrong marker for post-mitotic cells concluded that they are present in tissues of older donors in increasing amounts. The marker used was the lysosomal beta-galactosidase enzyme (Dimri et al 1995); however, lysosomal enzymes increase during a long resting stage regardless whether it is reversible or irreversible (Macieira-Coelho et al 1973) hence they are not appropriate to identify post-mitotic cells. The latter were called senescent cells and investigators went on studying them believing they were studying cell aging when in fact they were studying pathology.

Indeed these cells can be seen in the tissues of patients with different pathologies. Atypical fibroblasts were described in arthritic cartilage of old animals the cells seemed to be atypical in function and in structure (Siberberg et al 1964; Weiss 1975). Moreover, smooth muscle cells from the fibrous plaques of arteries have a decreased growth response to whole–blood serum analogous to that observed in cells in culture at the end of their proliferative life span (Ross 1986). Several markers could detect the terminal cells in other pathologies. They were present in the skin of a 35 years-old with diabetes, hypertension, and psoriasis, of two patients with Werner's syndrome, of a 96 year-old, an age where different pathologies are inevitably present (Puvion-Dutilleul and Macieira-Coelho 1983), of patients with Xeroderma pigmentosum, Cockayne syndrome (Puvion-Dutilleul and Sarasin 1989), with diabetes and kidney disease (Morocutti et al 1996; Uziel et al 2007), with venous ulcers and venous hypertension (Mendez et al 1998), post-radiation fibrosis (Herskind and Rodemann 2000), liver cirrhosis (Wiemann et al 2002), and AIDS (Cohen and Torres 2017).

On the other hand different markers could not detect the post-mitotic cells in normal human tissues: morphology of 30 nm chromatin fibers (Macieira-Coelho 1991), telomere length (Allsop et al 1992), expression of genes involved in cell cycling (Grassilli et al 1996), expression of the EPC-1 quiescence specific gene (Pignolo et al 1993; Tresini et al 1999), gene profile determined by cDNA microarrays (Park et al 2001) none could detect the post-mitotic cells in normal tissues of human donors.

Obviously we do not age because our cells stop dividing, indeed cells from tissues of old donors retain their capacity to divide (Maier 2007).

The interesting finding that post-mitotic cells become apparent only in pathological processes was overlooked. Since eliminating the so-called senescent cells improved aging of some animals some investigators thought this proved the rational for approaching this way the mechanisms of aging. Controlling atherosclerosis will improve aging but the mechanisms causing it do not concern the mechanisms of aging. The same can be said of other diseases. In spite of the evidence investigators persist in using the post-mitotic cells to study human senescence, which is aggravated by causing them"senescent cells" - a misnomer.

The Search for Universal Causes of Aging Common to All Organisms

The concepts concerning the mechanisms of aging have evolved with epistemology. There has been a tendency to explain aging in terms of a cause common to all organisms although the process does not evolve identically in all. In some organisms like the opossum (a small marsupial) or the salmon aging is a rapid process taking place after a short intense reproductive period; in other organisms such as the elephant and humans it is slow and progressive; finally in lobsters, some tortoises, and some fishes it is undefined. In spite of these differences and some obvious contrasts concerning several parameters between organisms (metabolic, genetic, histological, evolutionary, etc.) several gerontologists persist in extrapolating from one organism to the other attempting to find universal explanations. Some even extrapolate from unicellular organisms like yeast to humans.

Rodents are the laboratory animals most used in gerontology, however, there are fundamental differences when compared to humans. For instance the different morphology of chromosomes between species such as mice and humans suggest a fundamental different genetic organization that reflects on function. The recombination potential of mouse chromosomes is very impressive and does not decline with aging (Macieira-Coelho and Azzarone 1988); on the contrary human chromosomes are very stable and chromosome rearrangements decrease with aging (Bourgeois et al 1981), which has implications for differences in life span (Macieira-Coelho 2011).

From the evolutionary point of view the divergence between rodents and humans is 100 million years with repercussions on the mechanisms of aging, which evolved through natural selection.

This does not mean that comparative gerontology is useless. However, some mechanisms may be conserved but with the increasing complexity of the organisms new mechanisms develop improving the homeostatic regulation of life span. Moreover organisms with little or no cell renewal have other regulatory mechanisms than those where cell turnover continues throughout life.

Search for a Unique Cause of Aging

There is still a tendency today to consider one cause of aging followed by a cascade leading to senescence. This happened with the protein error hypothesis which in fact has a cultural origin based on the belief common to different cultures that humans are finite because of the accumulation of faults.

Other theories considered aging as the consequence of a cycle of expression and suppression of different genes. Evolutionary theories proposed that natural selection would preserve the expression of favorable genes before the reproductive period leaving the expression of the deleterious ones for after that period. Specific genes are still proposed today as the cause of aging and not long ago a single gene has been mentioned. A phenomenon as complex as aging cannot be due to a few genes, not even only to about the 1.5% of the fraction of the human genome that contains the expressed genes. A gene is not a single selfish identity; there are hierarchies of information in the genome upon which depends gene expression. Genes cannot be seen as autonomous entities, measurement of enzyme levels in lymphocytes of trisomic 21 patients illustrated this feature (Mellman et al 1964). Galactose-1-phosphate (GalP), acid phosphatases (Aps), and glucose-6-dehydrogenase (G6PD) levels were all increased in circulating blood lymphocytes of trisomic patients although the genes coding for these enzymes are not located in chromosome 21. The gene coding for GalP is located in chromosome 9, those for Aps on chromosomes 2, 3, 11, and 19, and that for G6PD on chromosome X. This work shows that the extra chromosome disturbed the whole genomic environment affecting the expression of genes in other chromosomes.

Moreover, there are epigenetic regulations that have become apparent and new regulations are being uncovered from redundant sequences without expressed genes that not long ago have been named junk DNA. Furthermore, there are examples of different survivals in the presence of the same genome. Female worker bees have rapid senescence and life spans of months, while queen bees of the same genotype have life spans of many years of active egg production. The difference is caused by exposure of larvae to nutrients and juvenile hormones (Finch and Tanzi 1997).

Some theories interpreted aging as the result of a depletion of a vital reserve. During the second half of the XX century Selye offered an interesting scientific interpretation of this concept based on his work on stress (Selye 1970). He proposed that the human organism has a limited adaptive capacity that is consumed by events that he called stress, which trigger a hormone response. Aging would be the result of the accumulation of all the stresses and the consequent compensatory responses through the existence of the organism. He could induce premature aging in rats with a hormone and prevent it with another hormone, which he called catatoxic – capable of cancelling the toxic effect.

The role of stress in pathology is well known it has a notorious effect on mortality, which becomes more pronounced with time as the amplitude of stress sufficient to kill the organism decreases with age. Events that cause stress at 40 years of age, which the organism can overcome may be fatal at age 80. On the other hand small doses of stress may have a positive effect on longevity. This has been observed in lower organisms where ionizing radiation in small doses could prolong longevity.

Some theories attempting to explain aging concentrated on metabolic reactions or one system when the phenomenon concerns the whole organism. This happened with the free radical and the immune theories. The free radical theory attempted to explain several parameters by a single mechanism – accumulation of free radicals, it was proposed as the cornerstone in gerontology - the theory of everything (Harman 1980). It was thought to provide an explanation for aging, for the different life spans of mammalian species, for the clustering of degenerative diseases in the terminal part of the life span, for the increase in autoimmune manifestations with age, and for the greater longevity of females.

The immune theory explained aging in terms of a decreased function when what happens is a reorganization of the immune response (Bonafé et al

2001). The structural and functional reorganizations of the human organism during the life span is a fundamental aspect of aging. The organism consists of different hierarchical structures: molecules – cells – tissues – organs – organism – psychic activity. As summarized by Schrödinger, the fundamental characteristic of life is the creation of order from order and the sole source of biological order is biological order. Information is transmitted through the structural hierarchy with increasing complexity, new properties emerging from each structural level(C.D. Broad 1973). Konrad Lorenz (1977) recognized information and energy transduction as two corner stones coupled in a multiplying interaction to assert the power of life. Leo Szilard demonstrated that information is equivalent to negative entropy, i.e. less disorder and more free energy available. The reorganization that takes place through the life span in the different hierarchical structures modifies function and the transfer of information.

Aging is a Consequence of the Second Law of Thermodynamics

I believe that there is no need to look for a particular cause of aging there is no alternative – aging happens by default (Macieira-Coelho 2016). The first step for survival in the biosphere is the capacity to meet energy requirements, life depends on the utilization and transduction of energy and thus has to follow thermodynamic rules.

The second law of thermodynamics states that in a closed system when energy is used to produce work it becomes more dispersed increasing disorder, reducing the probability of its long-term utilization, and increasing entropy. When two bodies at different temperature are in contact heat passes from the hotter to the colder one and does not come back, hence the second law implicates that the thermodynamic arrow of time is unidirectional.

It was mentioned above that structure and function are coupled and that information circulates through the hierarchical structures of the organism with new properties emerging from the increase in structural complexity. Structural changes evolve continuously through the organism life span and function evolves accordingly.

In a complex multicellular organism cell division starts with the zygote then drives it through the developmental stages. Division of somatic cells is the way to evolve towards their role in the organism. Once a cell reaches its final function, either it goes on dividing in the new state or becomes post-mitotic - in both cases it cannot reach a steady state. There is no division without modification of the cells; during DNA synthesis and separation of two new cells there are reorganizations in the different hierarchical organizations of DNA, which are unpredictable (Macieira-Coelho 1990). Telomere shortening is just one modification occurring in certain cells though not in all. Furthermore, DNA synthesis is asymmetric; because of the semiconservative synthesis of DNA, which was observed at the level of cell populations, it was thought that the two sister cells are identical. However, when division was studied in individual eukaryotic cells it was found that DNA synthesis and cell division are asymmetric (Macieira-Coelho et al 1982; Macieira-Coelho 1995; Macieira-Coelho 2007) leading to cumulative modifications. The apparent order observed when one studies a phenomenon globally disappears when it is studied at a lower scale. When a cell population divides there is a whole distribution of heterogeneity, which can keep going for a while but eventually the system collapses the distribution of DNA between sister cells becomes chaotic suggesting a phase transition (Macieira-Coelho 1995, 2007).

When in post-mitosis a steady state cannot exist either; at the molecular level all is fuzziness, uncertainty and probabilistic, which increase the further one goes down the scale. A cell that would metabolize remaining exactly identical cannot exist. At the molecular level metabolism depends on energy transduction for the induction of the right molecular conformations to perform biochemical reactions. Molecular conformation is assumed by gradients of electrical potential created by the transfer of electrons, protons and ions and by phosphorylation, which activate energy barriers. There is a decreased mitochondrial oxidative phosphorylation that impairs cellular metabolism (Lesnefskyad and Hoppelbebc 2006). During cellular senescence ATP content decreases following exposure to metabolic poisons, showing a defect at the point of origin of inorganic phosphate (Muggleton-Harris and Defuria 1985). The pathways of the phosphorylation cascade initiated at the cell periphery are impaired. Qualitative modifications of the phosphorylation of some proteins and a relative decrease of others were observed with the presence of new isozymic forms of protein kinases and new phosphoproteins (Kahn et al 1982).

Molecules assume a distribution of conformations with different efficacies (Cantor and Schimmel 1980), the modifications in phosphorylation raise the possibility that there is an increasing probability of not all molecules having the adequate functional shape. The biology of conformation wears down during aging (Macieira-Coelho 2015), which is one of the reasons why function becomes increasingly inadequate. The deterioration of conformational flexibility occurs at all hierarchical levels of structure in an irreversible way.

When one goes down further at the molecular level uncertainty becomes more pronounced, at the particle level life is driven on the quantum edge (Al-Khalili and McFadden 2014). For instance DNA replication depends on base pairing which is provided by hydrogen bonds obtained with shared protons (the nuclei of hydrogen atoms). This base pairing is ruled by quantum mechanics, i.e. by uncertainty that originates infidelity; enzyme reactions are also driven on the quantum edge (Al-Khalili and McFadden 2014).

Highlights

The second law states that all systems spontaneously change in such a way as to decrease their capacity for subsequent change. A steady state does not exist in living organisms, living means continuous adaptation through change away from equilibrium. A system driven by the utilization of energy, going through a permanent restructuring, has to follow the second law with an inexorable increase in positive entropy, tending to a limit. The flattening of the mortality curve in elderly people is the expression of the final decrease in available energy and increase in entropy that constitute a barrier to the human longevity.

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