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Theory of aging and cell senescence

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Abstract: The process of aging is an irreversible one in which an organism undergoes various changes over time. Although some scientists may use the terms "aging" and "senescence" interchangeably, others differentiate between the two. Cells go through the aging process only at the end of their lifespan, while they can undergo the senescence process at any point in their life. Thus, as aging is a natural process, most organisms cannot prevent it. So there are some main questions why and how does aging occur?

Keywords:aging, cell senescence, aging of organs, lifespan, life expectancy, aging theories, programmed aging theory, error or damage theories, non-aging system.

Introduction: Aging is one of the puzzling topics in natural science, causing debates in different areas for a long time. In the current review, we will discuss the main aspects of the aging process, including aging theories, and cell senescence.

Aging

Aging or senescence is a natural process where an organism goes through physical and psychological changes over time [1] while increasing an organism's vulnerability to disease and environmental interactions [2].

When does the human body begin to age? The biological aging process of the human body typically begins after we reach adulthood, around the age of 20. At the cellular level, aging starts around the age of 25, with the first signs appearing on the skin such as wrinkles, dry skin, and changes in texture, usually when we approach 30 years of age. Around this same age, the brain also ages, with a gradual loss of neurons leading to memory loss and difficulty concentrating over time.

The heart starts to age around the age of 40, which is why we tend to see more cases of cardiovascular disease after this age. As we age, the elasticity of our blood vessels decreases and lipid compounds may start to accumulate on the walls of the arteries, particularly for those with a genetic predisposition or who had an unhealthy diet during their youth.

Similarly, lung capacity begins to decline around the age of 35-40 and may only be at 50% by the time we reach 70 years old. Our kidneys also lose about 50% of their ability to filter waste by this age.

However, the liver is considered the strongest organ when it comes to aging. As long as it is not affected by infections, excessive alcohol or sugar consumption, or drug use, the hepatocyte has an excellent ability to regenerate and can remain young until it reaches 60-70 years old [3].

Why does the human lifespan have a limit?

Aging is a phenomenon of functional decline and disease risk. It is important to understand the difference between life expectancy and maximum lifespan.

Life expectancy refers to the average number of years a person can expect to live, while life span is the maximum number of years a human can live. Although the maximum life span has been around

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125 years for the past 100,000 years, life expectancy has greatly increased by about 27 years in the last century, particularly in Western countries [4].

Throughout human history, life expectancy at birth has rarely exceeded 30 years. This was mainly due to the high rate of childhood mortality. Before the Industrial Revolution, famine and infectious diseases were the leading causes of death. However, since then, there has been a significant shift in the factors contributing to mortality. Improvements in agriculture, food storage, and transportation have eliminated famines in Europe and the United States. Better food security and living conditions have reduced the prevalence of infectious diseases. Infant mortality rates have decreased, and non-communicable diseases such as heart disease, cancer, Alzheimer's, and diabetes have become more common [5].

We still know little about the causes of human aging as the ultimate mechanisms that limit life span, but the most likely explanation resides in the logic of life itself, which is based on turnover, with genetic variation and natural selection as the mechanisms that gave rise to the bewildering diversity of life on our planet. Because the life span of a species is linked to life history strategies, a species does not need to live for eternity to thrive, which essentially rules out a selection of perfect living systems. Hence, aging is likely due to imperfection, imperfection at the molecular, cellular, and physiological levels [6].

Cell senescence

Are “cell aging” and “cell senescence” the same thing? This question is highly debated in the modern science fields. However, both terms are used indifferently, describing their own individual concepts [7].

Strehler (1982) interpreted senescence as “[…] changes that commonly occur in the post-reproductive period, resulting in decreased survival capacity of individual organism” [8].

Senescent changes typically occur during the later stages of life and are often associated with increased mortality, which is a common characteristic of this stage. Although the terms "aging" and "senescence" are often used interchangeably, the differences between them may be more a matter of emphasis rather than concept [9].

Senescence is a process where cells stop growing due to damage caused by DNA damage, telomere shortening, telomere dysfunction, or oncogenic stress. This growth arrest is irreversible and helps to suppress potentially dysfunctional, transformed, or aged cells. The word senescence comes from the Latin word senex, which means "growing old." [10].

After telomeres were discovered, it was found that cell division is limited by telomere erosion, which occurs during DNA replication in a phenomenon known as the "end-replication problem".

A few years ago, it was discovered that cells can experience rapid senescence that doesn't depend on telomere shortening. This is referred to as stress-induced premature senescence or SIPS. Various types of stress can cause a quick and irreversible halt to cell division, which typically takes several days in culture, compared to the weeks or even months it takes for replicative senescence to occur [11].

There are noticeable differences between men and women in terms of how certain diseases affect them. These differences can be seen in the frequency of occurrence, the symptoms experienced, and the predicted outcome. As we age, conditions such as frailty, neurodegenerative disorders like Alzheimer's and Parkinson's, mood and anxiety disorders, cancer, mild traumatic brain injury, and

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dysfunction in various organ systems may occur. These dysfunctions include osteoarthritis, hepatic steatosis, liver fibrosis, and atherosclerosis. On average, women have a longer life expectancy and a lower risk of developing cancer and Parkinson's disease compared to men. However, they are also at a higher risk of developing Alzheimer's disease, more likely to be diagnosed with depression, and more likely to experience worse symptoms after a mild traumatic brain injury. Currently, there is a lack of research on the molecular basis of sex differences, and the studies that have been conducted (mostly in relation to neurological diseases) have mostly focused on the neuroprotective properties of sex hormones. These properties include protecting against oxidative stress, promoting neuron viability, and combating excitotoxic events. However, recent studies suggest that cellular senescence may be the underlying biological factor behind sex differences in both neurological and non-neurological diseases [12].

Aging theories

Many theories are currently trying to explain aging processes, and many biomarkers have been identified to measure aging and its evolutionary stages. Approaches and biomarkers are not studied to extend life span but to guide therapeutic choices and optimize patient management and personalization of care.

There are various theories about the aging process, but none of them seem to be entirely satisfactory. Traditional theories suggest that aging is not genetically programmed or an adaptation. Theories of aging are generally classified as either program or damage theories [13]. Programmed theories suggest that aging follows a biological timetable, which might be linked to the regulatory system that manages childhood growth and development. This system could be influenced by changes in gene expression that impact the body's maintenance, repair, and defense mechanisms. Damage or error theories, on the other hand, emphasize that environmental factors can harm living organisms and lead to cumulative damage at different levels, causing aging [14].

There are three sub-categories of the programmed theory of aging. The first is Programmed Longevity, which suggests that aging is caused by genes turning on and off in sequence, leading to the manifestation of age-related deficits known as senescence. The second sub-category is the Endocrine Theory, which proposes that biological clocks control aging through hormone regulation. Recent studies have shown that aging is indeed hormonally regulated and that the insulin/IGF-1 signaling pathway plays a crucial role in this regulation. According to the Immunological Theory, the immune system becomes weaker as we age, making us more susceptible to illness and ultimately leading to aging and death. It is well-known that the immune system is most effective during puberty and gradually declines with age. As we get older, antibodies become less effective and the body is less able to combat new diseases, which can cause cellular stress and eventually lead to death. Research has linked an imbalanced immune response to various conditions including cardiovascular disease, inflammation, Alzheimer's disease, and cancer. Although the exact causal relationships between the immune system and these conditions are not fully understood, the immune system is considered to play a significant role in their development.

The theory of damage or error in aging can be divided into five main categories. The first is the wear and tear theory, which suggests that cells and tissues in the body have vital parts that inevitably wear out over time due to repeated use, leading to aging and eventually death. This theory was first introduced by German biologist Dr. August Weismann in 1882 and remains a popular explanation for aging even today.

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The second theory is the rate of living theory, which proposes that an organism's life span is directly related to its rate of oxygen basal metabolism. While this theory is helpful, it does not fully explain the maximum life span. Dr. Rollo has proposed a modified version of Pearl's rate-of-living theory, which emphasizes the hard-wired antagonism of growth (TOR) and stress resistance (FOXO).

The cross-linking theory of aging was introduced by Johan Bjorksten in 1942. This theory suggests that an accumulation of cross-linked proteins can damage cells and tissues, slowing down bodily processes and resulting in aging. Recent studies have shown that cross-linking reactions are involved in the age-related changes in the studied proteins.

The free radicals theory of aging, which was first introduced by Dr. Gerschman in 1954 and developed by Dr. Denham Harman, proposes that superoxide and other free radicals cause damage to the macromolecular components of the cell, leading to accumulated damage and eventual malfunction of cells and organs. The body possesses natural antioxidants in the form of enzymes, which help to curb the build-up of free radicals. This theory has been supported by experiments in which rodents-fed antioxidants achieved greater mean longevity.

The somatic DNA damage theory suggests that DNA damages occur continuously in the cells of living organisms and while most of these damages are repaired, some accumulate over time. Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction. Damage to mitochondrial DNA might lead to mitochondrial dysfunction, and aging is the result of damage to the genetic integrity of the body's cells [14].

Is aging a Universal Trait?

Is there such a thing as a non-aging (forever young) system? In theory, in a fundamental sense, such a system cannot exist, for cosmologists generally agree that our universe and solar system have a finite life span. On the other hand, physicists agree that most subatomic particles (perhaps even protons) – decay. So if both the universe and its matters change through time and age, then so must all the intermediate organization levels. Despite this logistic explanation, non-aging systems do exist [15].

The great majority of animal species undergo the process of aging [16]; it is widespread but not universal, and some organism species can somehow avoid the aging process. While many species do age, there are some that exhibit 'negligible' senescence, meaning they show little to no signs of aging with increasing age. Some species could theoretically even show 'negative' senescence, meaning that they could experience physiological improvement with age. For example, freshwater polyps of the genus Hydra exhibit no decline in survival and fertility as they age. Moreover, certain plants display no signs of aging; a few trees, for instance, can live for thousands of years [17].

Aging is a natural and inevitable process that occurs in all living organisms (except the organisms with unique evolutionary adaptations where they can avoid the aging process), and it can be considered a universal trait. While the rate and specific manifestations of aging may vary across species, the fundamental principles and mechanisms of aging are observed universally.

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