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Biological theories of aging

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Introduction

Health care providers are well acquainted with the age-associated increased risk of illness and death among their elderly patients. Commonly defined as the accumulation of diverse deleterious changes with time, aging exponentially increases the risk of death. By age of 80 years, the relative risk of dying is more than 300 times greater than for someone aged 20 years. Despite the inevitability of aging and its importance to health, how and why we age remains a poorly understood aspect of human biology.[1]

By 2030, about one in five American will be over age of 65 years, making the consequences of aging a great challenge for future physicians. As a population ages, age-associated diseases exact a disproportionate burden of morbidity and mortality. Although most clinicians anticipate that lifespan extension will mean a higher incidence of illnesses such as Alzheimer's disease, scientists find that in simple organisms mutations that slow aging also postpone age-related disease.[2] This suggests that understanding the aging process might yield treatments that delay or avoid the ills of aging such as Alzheimer's disease, heart failure, osteoarthritis, and stroke. However, despite more than 300 theories, no single theory fully explains aging.[3] While it would be thrilling to find a single unifying explanation for aging, most experts believe aging is a complex and multifactorial process.[4] The multiple aging theories are not necessarily mutually exclusive and most likely several processes act together to contribute to how and why humans age. Some mechanisms likely contribute to different degrees in different individuals. While aging theories remain unproven, the public and marketers embrace some such as the free radical theory of aging (FRTA), and use it as a basis to promote antiaging products aimed at neutralizing free radicals. Yet to date, there is no evidence that any supplement or product stops the aging process.

This article will explore several common theories about why and how we age. By understanding current aging theories, clinicians can follow advances in aging research and intelligently address patient questions about life extension therapies and strategies to slow aging.

Why do we age?

One challenge is to explain why aging occurs despite its apparent detrimental effects. Characterized by a progressive loss of function, aging increases an organism's vulnerability to

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disease and the environment.[1] Since natural selection favors survival of the fittest individuals, this poses the question why natural selection did not eliminate something as detrimental to an organism as aging. Several different theories attempt to explain this paradox although each shares the concept that aging results from a decline in the force of natural selection.

In 1890s, Weisman proposed that aging evolved to the advantage of the species and not the individual. He argued that natural selection eliminates older members of a population so that they no longer compete with younger generations for resources, paving the way for younger members to survive and reproduce. So while aging compromises an individual, evolutionarily the species benefits. He further postulated that cell death is a programmed event that somatic cells undergo a specific number of divisions, and these division limits differ among species with the number of programmed divisions correlating with life span. Later, Hayflick found evidence supporting a cell division limit when he discovered that human fibroblasts grown in cell culture replicate a finite number of times before they age and die, a process he named replicative senescence.

In 1952, Peter Medawar developed the accumulated mutation theory and the concept that aging results from the accumulation of somatic cellular damage and damage to "repair" genes coding for functions such as DNA repair. Medawar recognized that most wild animals succumb to the environment, from predators, disease or accidental death, well before attaining old age. Since living beyond the age of reproduction provides only a limited advantage in offspring numbers, natural selection selects out harmful mutations expressed early in life but exerts little evolutionary pressure to rid organisms of mutations causing detrimental effects at an older age.

In 1957, Williams introduced the concept of antagonistic pleiotropy.[1] Antagonistic pleiotropy proposes that some genes have more than one effect (pleiotropy) and that some effects might benefit early survival but cause harm later in life (antagonism). In essence, these genes escape the force of natural selection by offering the tradeoff of a survival advantage early in life at the cost of harm at an older age. For example, genes enhancing oxidative processes may generate damaging free radicals that age an organism but offer a survival advantage in youth by generating greater muscle effectiveness that allows an organism to escape predators. High levels of testosterone in men is another example, where the increased aggression and strength associated with testosterone allows males to dominate and mate more frequently although it may shorten the male lifespan by increasing the risk of atherosclerosis.[5] Antagonistic pleiotropy may also explain the Hayflick limit of cell division. Early in life, limits on cell division may suppress tumor growth[6] but exact the price of cellular senescence later in life. In effect, the Hayflick limit may represent an evolutionary tradeoff of tumor protection in youth at the cost of aging. Antagonistic pleiotropy may also explain why harmful genes like the Huntington's disease (HD) gene remains in the gene pool. The HD gene may exert a positive effect early in life that favors natural selection, while its harmful effects occur after the reproductive years are over, allowing the gene to escape natural selection.

While similar, there are differences between mutation accumulation and antagonistic pleiotropy theories. In the mutation accumulation theory, harmful genes passively accumulate from generation to generation. In the antagonistic pleiotropy theory, genes related to aging have an early positive effect and are actively retained in the gene pool. However, these theories are not mutually exclusive and both mechanisms may contribute to why we age.

In 1972, Kirkwood[1] proposed a third explanation for aging, the "disposable soma theory." According to the disposable soma theory, organisms balance the need for the repair and maintenance of somatic cells with the resources needed for successful reproduction. Since resources are not limitless, organisms must preferentially direct resources to support early survival and reproduction at the expense of repairing and maintaining somatic cells. In essence, an organism needs to perpetuate the species and after reproducing, the soma or "body" is disposable. Organisms eventually age because accumulated damage and incomplete repair leads to a greater susceptibility to disease and environmental stress.[7] Fruit fly studies demonstrate that destroying germ cell lines extends their lifespan provide some scientific evidence to support the disposable soma concept.[8]

Causes of aging

Theories about what causes aging generally fall into one of two groups, genetic or stochastic. Genetic, or programmed theories, propose that aging is genetically determined and organisms have an internal clock that programs longevity. Damage theories, sometimes referred to as stochastic theories, propose that chance error and the accumulation of damage over time cause aging. Stochastic theories include wear and tear, error catastrophe, free radical theory, DNA damage hypothesis, loss of adaptive cellular mechanism, and the mitochondrial theory.

Programmed theories

Genes undoubtedly contribute to longevity although the extent of genetic versus non-genetic factor contributions to aging remains uncertain.[9] In humans, twin studies estimate that genes contribute about 20–30% of aging,[10] but it is not yet clear how genes account for this variability. According to programmed theories, an internal biological clock regulates development, growth, maturity, and aging by sequentially switching genes on and off.[4] Proponents of programmed longevity point out that despite significant increases in life expectancy, the maximum human life span remains unchanged. That genes play a role in longevity is clear[2] and scientists have identified several gene mutations affecting life span in a wide range of model organisms. In roundworms, genetic mutations that double the lifespan provide clear evidence that genes influence aging and longevity. However, no single identified gene completely controls aging, consistent with the concept that the genetic control of aging is multifactorial. Scientists postulate that "aging genes," exert their effects by slowing or stopping biochemical metabolic pathways.[11] Metabolic pathways emerging as important to the aging process include the insulin/IGF-1 and targets of rapamycin (rTOR) pathways, although the mechanisms of how these pathways control aging remain unclear.

The Hayflick limit is viewed as an example of programmed aging. Hayflick found that human fibroblasts grown in culture stop dividing after about 50 cell divisions and undergo what he describes as "replicative senescence." He also found that fibroblasts taken from older individuals stop dividing after fewer divisions than those taken from younger individuals and that the lifespan of a species roughly correlates with the replication limit. Telomeres, which are protective caps at the ends of chromosomes, shorten with each cell division until cells stop dividing and may represent the timing mechanism that explains the Hayflick phenomenon. Telomere shortening may also be an example of antagonistic pleiotropy, protecting against the runaway cell division and abnormal growth associated with cancer but at the price of aging.[12] Stress, especially oxidative stress, speeds telomere shortening and telomere dysfunction is characteristic of premature aging syndromes. For example, a mutant enzyme required for the efficient replication and stabilization of telomeres characterizes Werner's syndrome, a form of progeria.[8]

Telomerase, an enzyme that prevents telomere shortening, is expressed by immortalized cells but is absent in normal somatic cells. The connection between cell division and telomeres makes telomerase an area of intense research interest. Telomerase is upregulated in 85–95% of cancer cells and developing telomerase inhibitors exhibits promise as a potential cancer therapy. On the other hand, stimulating telomerase might useful to promote wound healing or to slow aging.[12] As an antiaging therapy, the dilemma is how to activate telomerase sufficiently to extend critically short telomere in "old cells" without inducing abnormal growth. Despite its appeal, several inconsistencies with the telomere theory emerge. For example, telomere deficient mice seem to age normally and some short-lived animals have long telomeres.

The neuroendocrine system plays a key role in orchestrating an organism's growth and metabolism. The neuroendocrine theory proposes that programmed functional changes in neurons and associated hormones are central to the aging process.[5] Examples of neuroendocrine programming include pubertal changes and menopause in women. One version of the neuroendocrine theory holds that the hypothalamic–pituitary–adrenal axis (HPA) is the pacemaker that

directs the onset and termination of each life state and that age-related HPA changes impair homeostatic mechanisms causing age-related physiologic changes.[4] The age-related changes in pituitary, adrenal, and gonadal hormone production led many clinicians to prescribe hormones off-label as an antiaging therapy.[13] However, in the absence of a documented deficiency, the use of hormones to delay aging is controversial. In 1990s, clinicians commonly prescribed hormone replacement therapy (HRT) to delay age-related changes associated with menopause. However, the Women's Health Initiative (WHI) found that HRT resulted in a higher risk for breast cancer, stroke, cardiovascular disease, and thromboembolic events, thus limiting its use as an antiaging therapy. For men, testosterone increases muscle mass and perhaps vitality but in the absence of a documented deficiency many clinicians hesitate to prescribe supplemental testosterone (TRT) because of its side effect risks. Currently, the American Association of Clinical Endocrinologists recommends TRT only for those men with a documented testosterone deficiency and symptoms consistent with a testosterone deficiency.[14,15]

Somatopause, or the age-related decrease of growth hormone and the insulin-like signaling pathway, appears to play a role in regulating lifespan. Insulin-like signaling activity and the expression of insulin-like peptides are reduced in long-lived nematodes, mice, and humans. Centenarians are generally more sensitive to insulin, and mutations in IGF-1 receptors are overrepresented in a cohort of Ashkenazi Jewish centenarians.[2,16] In nematodes, mutations that decrease the activity of daf-2, a gene that encodes for a hormone receptor similar to mammalian insulin and IGF-1, more than doubles a nematode's lifespan.[2] In humans, insulin resistance, changes in body composition, and physiologic declines in growth hormone, insulin-like growth factor-1 (IGF-1), and sex steroids characterize the aging process. Inactivating insulin/insulin-like signaling increases lifespan in nematodes, fruit flies, and mice suggesting that this system is a critical part of the aging process. Metformin that decreases insulin resistance can increase the life span and inhibit carcinogenesis in rodents suggesting that it may be an effective antiaging agent.[17]

The marked decrease in growth Hormone (GH) secretion with age results in a decline in ICF-1 levels, which is associated with conditions such as heart disease, sarcopenia, osteoporosis, and frailty associated with functional decline. The adverse effects of low GH provide the rationale for prescribing GH as an antiaging hormone. However, GH supplementation for older healthy adults is controversial with unclear benefits and the potential for serious side effects. Further research about GH and the insulin/IGF-1 pathway may provide insight into therapies designed to slow the aging process.

Age-related decreases in DHEA levels cause an "adrenopause" phenomenon, characterized by low DHEA and normal to high cortisol levels. Cortisol may be toxic to neural cells, adding to the disruption of the HPA and in the lay press some label cortisol the "death hormone."[18] Replacing DHEA is often touted for antiaging, but despite the apparent positive effects of DHEA on muscle, bone, cardiovascular disease, and sexual function, few studies are large enough and/or long enough for conclusions regarding its effects on aging. At this time, physicians should counsel patients taking DHEA that its long-term benefits and safety remain uncertain.[19]

Some postulate age-related changes in the immune system, or immunosenescence, is responsible for aging. Observations supporting this theory are an age-related functional decline of the immune system, an increasing level of autoimmune phenomena and the involution of the thymus gland. An important immune gland, the thymus peaks in both size and function during puberty and then progressively atrophies with age, producing fewer mature T cells. One interpretation of immunosenescence is that it represents a tradeoff between its decreasing usefulness once the repertoire of T cells has been set up and the resource cost of maintaining the organ.[20] As the immune system declines, an organism becomes more susceptible to infection. In addition to vulnerability to infection, immune dysfunction is linked to an increased risk of cancer, Alzheimer's disease, and CVD.[21]

Stochastic theories of aging (STA)

STA propose that aging is the result of the inevitable small random changes that accumulate with time and the failure of the body's repair mechanisms to fix the damage. Eventually, the

accumulated damage injures cells and tissues, contributing to the age-related declines in an organ's function.[5] Weisman first introduced the concept of accumulated damage as the "wear and tear" theory that likens an organism to a machine that "wears out" with time, use and damage from accidents, disease, and other hazards. A common example of wear and tear is osteoarthritis where the cushioning joint cartilage becomes less resilient with age, leading joints to develop arthritic changes. Aging teeth where dentin wears away with age and use are another example. However, unlike machines, living organisms can repair damage and the wear and tear theory overlooks an organism's ability to repair damage. Another argument against wear and tear is that animals living in protected environments still age without any increase in their maximum lifespan.

Free radical theory of aging (FRTA)

The FRTA is one of the most popular aging theories and forms the basis for many antiaging products and strategies. Free radicals (FRs) are highly reactive molecules that react with organic molecules in a destructive way. Reactive oxygen species (ROS), the most abundant FR found in humans, occur both as a by-product of normal metabolism and from external sources. First proposed by Harman in the 1950s,[22] the FRTA hypothesizes that aging is due to the accumulation of oxidative damage to lipids, DNA, proteins, and tissue by free radicals (FR). In the early 1970s, scientists recognized that mitochondria generate most FRs and proposed that FR damage to electron transport chain enzymes causes physiologic decline.[22] Mitochondria lack DNA repair enzymes, making mitochondrial DNA more susceptible to damage. The damaged mitochondria are more liable to produce free radicals creating a vicious cycle of mutation and FR formation that leads to increased cellular damage and senescence.[23] However, opponents to the mitochondrial theory point out ROS are a normal product of intercellular metabolism and despite their bad reputation, play an essential role in cellular health. The Framingham Longevity Study of Coronary Heart Disease found that longevity is more strongly associated with the age of maternal death than of paternal death suggesting that mitochondrial DNA is linked to longevity.[8]

Enzymes such as superoxide dismutase can neutralize free radicals by catalyzing reactions that convert ROS to water and oxygen. Nonenzymatic antioxidants, such as vitamins A and C, and phytochemicals such as flavonoids and carotenoids that occur naturally in foods, also neutralize free radicals. The idea that FRs promote aging suggests that interventions to limit their formation might slow aging. However, while there is evidence oxidative damage accumulates, it is not evident that the process contributes to aging in all organisms. Surprisingly, in some animals, genetic mutations that adversely affect superoxide dismutase actually increase longevity. Similarly, despite the theoretical benefit of reducing FR damage with supplemental antioxidants, there is scant evidence demonstrating the benefit of antioxidant therapy. Currently, the only conventionally accepted antioxidant therapy is for macular degeneration. Since smoking generates free radicals, researchers speculated that tobacco induces lung cancer by free radical damage and developed a trial to test whether the antioxidant beta-carotene lowered cancer risk in smokers. Researchers stopped the randomized trial early because the group receiving beta-carotene developed significantly more cancers than the control group. It may be that modifying aging requires an ideal balance of oxidants, antioxidant, and biomolecules rather than a disproportionate level of antioxidants.

A related theory is the DNA damage hypothesis, which posits that incompletely repaired free radical-derived damage alters gene expression and impairs cell function. Evidence supporting this theory includes studies connecting DNA repair ability to lifespan and premature aging to genetic mutations that damage DNA repair ability.

Energy restriction and lifespan

The rate of living theory proposes that organisms have a finite amount of calories to burn over a lifetime and that energy expenditure is inversely proportional to lifespan. When comparing

species, tiny mammals with rapid heart rates, such as mice, that metabolize oxygen more rapidly typically have shorter lifespans than animals who utilize oxygen more slowly. Some insects, nematodes, and fish demonstrate an increase in lifespan when their habitat temperature is elevated, and they have lower energy expenditure to maintain body temperature. The connection between energy expenditure and longevity may explain why calorie restriction extends lifespans in a diverse group of organisms ranging from single cell yeasts to mammals such as rodents. In some animals, reducing calories by one-third yielded a 40% increase in lifespan. Proposed mechanisms include the down regulation of the insulin/IGF-1 pathway and activating the sirtuin and the rTOR pathways. Sirtuin genes are present in all species and help regulate metabolism. Scientists at MIT found that inserting an extra sirtuin gene in yeast extended their lifespan although the mechanism remains uncertain.[24] Resveratrol, naturally found in grapes, activates the sirtuin pathway and appears to improve the health of aging mice. Unfortunately, resveratrol does not seem to be as helpful in humans.[25] The rTOR pathway is an abbreviation for the mammalian target of rapamycin. Rapamycin, a macrolide drug used to suppress the immune system, to treat cancer and to prevent restenosis after cardiac surgery,[26] increases longevity in several animal models. As the name implies, rapamycin inhibits TOR kinase. Unfortunately, rapamycin's side effects including hyperglycemia, dyslipidemia, immunosuppression, vasospasm, and renal failure limit its use in humans.[27] The data that energy reduction extends life is less compelling for primates[28] and for some primate species; calorie restriction does not appear to increase lifespan. In humans, most individuals find the 30–40% decrease in calories needed to extend life difficult to sustain over time. Even so, there is an abundance of literature promoting CR as a means to live longer and some patients will attempt CR. However, CR requires careful planning and appropriate patient counseling. Associated concerns with long-term calorie restriction include an increased risk of osteoporosis, fatigue, and loss of muscle mass.

The cross-linking theory of aging

This theory posits that aging results from glucose binding to proteins, which impairs their biological functions. Protein cross-linking is associated with the connective tissue hardening, cardiac enlargement, and renal disorders. Sugars bound to DNA can cause replication errors leading to malformed cells and an increased risk of cancer. Some endocrinologists view diabetes as an accelerated aging process and point out that individuals with diabetes have 2–3 times as many cross-linked proteins when compared to healthy age-matched controls.

Conclusion

Aging research seeks to gain an insight into a process that leads to increased fragility and vulnerability. Despite attempts to demystify the aging process, no single gene or decline in a biochemical system accounts for all aspects of aging. Currently, most researchers view aging as a complex multifactorial process with a likelihood that several processes work in concert. While in experimental data from animal models shows that aging can be modified, to date no known intervention slows, stops or reverses the aging process in humans. In fact, researchers find some treatments such as supplemental antioxidants to be harmful. However, many patients will still seek advice from their primary care physicians about treatments found on the internet or new research. Science uses theories to explain the natural world and an understanding of aging theories provides a useful backdrop for a primary care provider to evaluate new information and to discuss aging therapies with their patients.

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