**THEORIES OF AGING A REVIEW**

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**Abstract**

Aging is a multi-factorial process and is determined by several regulators and organizations. It is altered by various genetic, biochemical regulations and other systems running simultaneously in intimate contact. Each system can create a direct or an indirect impact on the aging process. Many people have attempted to understand aging and to explain it according to their refinement and tradition.**1, 2**

The rate and progression of cellular aging is differ from person to person. Ultimately, aging affects the cells of every organ of the body and the changes can begin, leading to some impact on cells function. Around the age of 20, lung tissue begins to lose its elasticity, and rib cage muscles start to shrink. In the gut, digestive enzyme production diminishes, affecting the ability of food absorption properly. Blood vessels build up fatty deposits and lose their flexibility to varying levels, leading to atherosclerosis. Also, aging decrease sperm production, and the prostate become enlarged.**3**

This article is a trial to overview the aging process and its theories. Besides, to through more lights about the relation between aging and dying and how slowing the age advancing.

**Theories of aging**

Theories of aging are often difficult to characterize because many of them overlap each otherand are interrelated (network theories).They classified into Stochastic and nonstochastic one. Stochastic theories explain aging as events that occur randomly and accumulate over time. While, nonstochastic theories clarify aging as certain predetermined, timed phenomen a as programmed theory and immunity theory.**2**

**Stochastic (general) theories of aging:**

**Telomere theory**

Telomeres are the terminal parts of eukaryotic chromosomes. Their length in humans is 8-14 kB long. Telomere replication occurs late in the cell cycle. Aging has great influence and control on telomeres replication.They are called "molecular clocks" of the cell. During aging the telomere shortens to the critical stage and then cell division significantly decreases. However, telomeres could be persistent in the non-aging cells like cancer and germ line. 4,5

For quite a while, scientists believed that telomere shortening held the answer to human aging. They thought that it was a sort of “cellular clock” that might govern aging. However, there are some problems with this idea. In humans, not all types of tissue contains actively replicating cells. Also, telomere short­ening is not universal among species. In mice, telomeres are routinely lengthened by an enzyme called telomerase, which is rare in humans. Scientists have concluded that while telomeres and senescence may contrib­ute to human aging, they do not govern it.6

**Gene Theory**

The gene theory suggests that aging is programmed because of harmful genes within every organism. These genes grow to be active only late in life and modify the organism physiology in ways that result in its death**.3** These genes may be responsible for the functional and the structural changes associated with aging. These changes may stop cells from “living and dividing infinitely” after their fixed life span**.7** Gene theory suggests that human life span is an inherited trait. Some studies on twins supported that there is a considerable similarity in time of death in monozygous twins**.8**

**Gene Mutation Theory**

This theory hypothesized that damaged DNA could be repaired by some enzymes within the cell. These enzymes removed the damaged region of the gene and add a new set of nucleotides, by utilizing undamaged strand as a template**.9** With age advanced, the gene repair mechanisms turn into less efficient and some mutations remain uncorrected leading to structural and functional aging changes (damaged DNA, mRNA and ribosomes). Accumulation of cells with altered structure and function resulting from these mutations may lead to malfunctions and eventual death**.10**

**Cross-linkage Theory**

Proteins are the building blocks of cellscomposed of peptides. Protein denaturation is an irreversible process. Protein denaturation is attributable to the formation of cross-links between peptide strands, causing structural and functional alterations. Aging and formation of new cross-links lead to irreversible alteration in the structure of some proteins of the cells. This protein dysfunction alters normal organ function (e.g., enzymes and collagen)**.11** Likewise, the glucose molecules attach themselves to the proteins, resulting in a chain of chemical reactions altering protein biological and structural roles. This process is called non-enzymatic glycosylation that induces Glycation End products (AGEs) formation. Production of AGEs induces many functional abnormalities by decreased enzymatic activity and reduced degradation of abnormal proteins.With advancing age, AGEs accumulate in area of collagen so the connective tissue becomes less elastic and stiffer. AGEs accumulate in hemoglobin and the eye lens and can interact with DNA interfering its repair**.12**

**Free Radical Theory**

An oxygen-free radical (OFR) is a derivative of the normal metabolism of the cells when they turn food and oxygen into energy. The free radical takes one electron from another molecule, which becomes unstable producing oxidative damage. Once OFR formed, these highly reactive radicals begin a harmful chain reaction. Their principal danger comes from their damaging reaction with important cellular components such as proteins, membranes or nucleic acids**.13** The gradual increase of these free radicals in the cells with time, may exceed their threshold concentrations contributing to the changes associated with aging**.14**

Antioxidants are the molecules that can safely interact with these free radicals and finish their chain reaction before the vital molecules are damaged.In aging cells, these anti-oxidants are either ineffective or saturated by high numbers of free radicals and loss their protective role. Also, the cells may produce fewer anti-oxidant substrates with advancing age**.7, 14**

This theory has been supported by experiments in which rodents fed antioxidants achieved greater mean longevity. However, at present there are some experimental findings which are not agreed with this early proposal. The review by Igor Afanas’ev shows that reactive oxygen species (ROS) signaling is the most important enzyme/gene pathway responsible for the development of cell senescence and organismal aging.15 Experiments attempting to reverse the effects of oxidative damage by feeding experimental animals dietary antioxidants, have not yielded conclusive results.6

**Cellular Garbage Theory**

According to this theory, there are gradual accumulation of inert substances including free radicals, aldehydes, histones, lipofuscins and amyloid bodies in the cells with aging. These substances interfere with normal cellular function by inducing deleterious changes in cellular components like proteins and nucleic acids. Amyloid bodies inside the nerve cells are the pathological hallmark of the Parkinson’s disease**.16**

Recent studies have provided evidences that there is a gene named PARK2 gene, which previously is implicated in Parkinson’s disease. This gene could delay the onset of aging and extend the life span of fruit flies by more than 25%**.17** Also, they postulated that PARK2 gene could have important implications for aging in humans. This gene encoded (Parkin) protein, that serves at least two vital functions; it marks the damaged proteins so that cells can discard them before they become toxic. Also, it is believed to play a key role in removal of damaged mitochondria from the cells. This process seems to decline with age**.18**

**Accumulation-of-Errors Theory**

According to this theory, random errors in the mechanisms of protein synthesismay result in accumulation of faulty proteins to levels that cause catastrophic damage to cells, tissues and organs. Any error in the formation of proteins (as enzymes) has considerable effects on cellular activities. Collection of errors-theory suggests that aging is attributable to a build up of multiple errors in protein synthesis with time.**19**

**Wear-and-Tear Theory**

Human being has a specific reaction to stress that differs according to age named General Adaptation Syndrome. Hans Selye (1936) mentioned that reaction to stress in child is in form of alarm reaction, in adulthood is resistence, while in senescence is exhusion. If the duration of stress is sufficiently long, the body eventually enters a stage of exhaustion, a sort of aging "due to wear and tear".

According to this theory, the cells and tissues of animals have vital parts that wear out leading to aging. Each cell has a specific amount of metabolic energy. The rate of energy that consumed could be determined animal’s lifespan**.17** Theory of depletion of available energy in cells is a contributing factor to aging changes. Reduction of caloric intake is considered most effective method to modify the rate of aging in rats. Old rats on this diet, behave and look like young ones.**20** These findings were experimentally recorded only and no standarized data in humans were proved.**21**

**Nonstochastic Theories:**

**Aging by Program (Programmed Longevity)**

Aging is caused by switching on definite genes and off over time. The major site of the localized aging chronometer is hypothalamus.The hypothalamus controls the production of certain growth the pituitary gland hormones**.22**Aging declines the ability of the organism to carry the message by reducing nerve conduction rates and modification of hormonal structure and amount. Also, receptors for nerve impulses or hormones may become less able to respond appropriately to incoming impulse or hormone**.23,24**

Alternatively, some researchers exclude the role of the central nervous system in programmed aging. They assumed that each normal cell type has restricted number of divisions and then it dies**.25,26** Fibroblasts that are taken from embryos divide 50 times, while those taken from adults only divides 20 times**.27** Also, cells isolated from patients suffering from Werner’s syndrome only divide 10-20 times. This syndrome is a condition in which the affected individuals show advanced signs of aging while still in their twenties.**28,29**

**Immunity Theory**

Immuno senescence is age-related functional diminution of the immune system include the following mechanisms; 1) lower rate of T-lymphocyte “killer cells” proliferation in response to a stimulus. 2) the changes include a decrease in humoral immune response, often predisposing older adults to decreased resistance to a tumor cell challenge and the development of cancer, decreased ability to initiate the immune process with increased susceptibility to auto-immune diseases.**30**

The autoimmune theory suggests that in advance of age the immune system is no longer able to perfectly distinguish foreign proteins from the body’s own proteins. Thus, auto-antibodies are generated that attack & destroy normal cells. Mutations of RNA or DNA bead to new antigens formation and consequently induce altered or new protein (foreign antigens) that stimulate the immune system against it.**31** Also, autoimmune reactions increase progressively with aging due to changes in antibody molecule by acquiring antigenic potential against the body and provoke the body’s immune system against various tissues**.32,33**

Indeed, dysregulated immune response has been linked to cardiovascular disease, inflammation, Alzheimer’s disease, and cancer. Although direct causal relationships have not been established for all these detrimental outcomes, the immune system has been at least indirectly implicated**.32**

**Aging and death**

Like aging, the death is a biological event that occurs due to breakdown in body function.**33**  In humans, causes of death are due to either weakened tissues of aged vital organs leading to troublesome of various physiological processes or malfunctioning of the body immune system that diminishes the resistance of body to different antigens. This contributes to more susceptibility to diseases and ultimately cause death**.25, 34**

**Prospective**

If the underlying cause of aging can be determined, it might be possible to interfere with the process and thus extending human longevity. So, the goal of increasing human lifespan can be achieved either by either suppressing the causes of death in younger people or delaying the aging process that causes us more susceptible to disease and death in older people**.25**

**Slowing down the aging process**

To slow down human aging, it is likely required to:eradicate some damaged or inactive molecules and cells and restore the function of several molecules and cells by repair or replacement**.25** Also, genetic engineering is the most powerful existing tool for the life extension by efficient and safe gene therapy that radically extends lifespan and prevents age-related pathologies35. It can help with renovation of the hypothalamus (the main neuroendocrine regulator), inhibition of the main aging pathways and stimulation of longevity pathways of most body cells and elimination of senescent cells.26,36

Telomerase gene delivery to old mice results in up to 20% lifespan extension in telomerase-treated mice.**37** In concert, these results prove the essential role of telomerase in delay the physiological aging and extend the longevity in normal mice through a telomerase based treatment**.5** Currently, the scientific community is suggesting that it capable of reversing the aging in human cells.

Actually, the free radical theory of aging raised a important form of research exploring the possible role of antioxidant nutrients in therapeutic or preventive strategies.38 Some literature reported an increased resistance to oxidative damage with chronic exercise and increased lipid, DNA or protein oxidation after perfoming exercise extremely39. However, a clear interpretation of studies regarding exercise-related DNA and protein oxidation, and lipid peroxidation is lacking.

Consistent physical activity has shown to oppose the alterations in body composition in older subjects possibly by increasing lean mass and reducing adipose tissue40, and to confer significant protection against several age-related diseases eg, diabetes;41 cancer;42 hypertension;43 and osteoporosis.44 Physical activity may still play an important role in restricting the free radical creation and oxidative damage. Physically active older persons induced adaptations in the cellular antioxidant defence systems.45

Nutritional supplementation, especially with antioxidants, has been frequently indicated as a potential to increase longevity.46 The theoretical basis supporting a possible relationship between antioxidant supplementation and longevity are mainly from the evidence showing a relationship of the latter with the rate of mitochondrial oxygen radical generation and the degree of unsaturation of membrane fatty acids.47 Indeed, these two molecular traits are significantly lower in all the relatively long-lived homeothermic vertebrates, and may be main causes of the low rate of aging of long-lived animals35.

**Modern reflection on theories**

In spite of recent advances in molecular biology and genetics, theories have been proposed to explain the process of aging, appears to be fully satisfactory.Theories which fall into the two main categories: programmed and error theories.

The programmed theory include; (1) Programmed Longevity and hormone regulation; the role of genetic instability in aging and dynamics of the aging process has been discussed,48 also, recent studies confirm that aging is hormonally regulated and that the evolutionarily conserved insulin/IGF-1 signaling pathway plays a key role in the hormonal regulation of aging.49(2) Autoimmune theory; definitely, dysregulated immune response has been linked to many age-related diseases, although direct causal relationships have not been established, the immune system has been at least indirectly implicated.50

The damage or error theory include; (1) Wear and tear theory, it sounds perfectly reasonable to many people (2) Cross-linkage and cellular garbage theories, an accumulation of cross-linked proteins damages cells, slowing down bodily processes resulting in aging. Recent studies show that cross-linking reactions are involved in the age related changes in the studied proteins. (3) Free radicals theory, at present there are some experimental findings which are not agreed with this early proposal. The review by Igor Afanas’ev shows that reactive oxygen species (ROS) signaling is probably the most important enzyme/gene pathway responsible for the development of cell senescence and organismal aging and that ROS signaling might be considered as further development of free radical theory of aging.15 (4) Somatic DNA damage theory has multiple interacting aspects. Recently, Michael Ristow's group has provided evidence that this effect is due to increased formation of free radicals within the mitochondria causing a secondary induction of increased antioxidant defense capacity.51A recent study shows that telomeres shorten with age in neural stem cells of the hippocampus and that telomerase-deficient mice exhibit reduced neurogenesis as well as impaired neuronal differentiation and neuritogenesis.52Taken together, these data indicate the link among gene mutation, telomere theory, brain aging and neurological diseases.

**Modifying the course of aging**

**(American Federation for Aging Research)**

1. Caloric restriction, in which labo­ratory animals are maintained on nutritionally balanced diets, containing 30 to 40 percent fewer calories than normal diet, has been shown to increase the average and maximum lifespans of organisms. It is currently under investigation in primates.
2. Experiments attempting to reverse the effects of oxidative damage by feeding experimental animals dietary antioxidants, , have not yield conclusive results. However, investigating oxidative damage remains one of the hottest areas of aging research.
3. More recent work with C. elegans, a roundworm, showed that changing just one gene related to metabolism could significantly extend the worm’s lifespan.

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