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Review Paper

A Review on Theories Regarding Ageing

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Abstract: Ageing and resulting senescence has been fascinating for scientists as well as common people. Ageing is an extremely complex multi-factorial process. Different types of morphological, physiological, biochemical, endocrinological and cellular changes are responsible for ageing. In this review, several theories are identified only briefly and a few (evolutionary, gene regulation, cellular senescence, free radical, and neuro-endocrine-immuno theories) are discussed in more detail. The multiplicities of mechanisms are examined also at the molecular, cellular and systemic levels to explore the possibility of interactions at these three levels. However, in spite of recent advances in molecular biology and genetics, the mysteries that control human life span are yet to be unraveled.

INTRODUCTION

Ageing is a progressive deterioration in structure and function of cells/tissues/organs/systems with age, so that there is decline in the rate of metabolism, ability to repair and resist infections. Different types of morphological, physiological, biochemical, endocrinological, cellular, genetic and molecular changes are responsible for ageing. It has been observed that the highly specialized cells undergo ageing at slower pace than the cells retaining their capacity for division eg, neurons age much slowly than epidermis. Different faculties start declining at different times eg, the number of germ cells reaches a maximum of 60×10^5 in each ovary by fifth month of intrauterine development. Before birth, a wide spread deterioration occurs and many oogonia disappear. New born female baby bears about 40,000 oocytes in each ovary but only 400 oocytes are shed at ovulation during the reproductive years of average woman. According to one's estimation, ageing causes a reduction of 12% in body weight, 15% in brain weight, 37% in liver weight, 20% in basal metabolic rate and 15% in velocity of nerve impulse.

THEORIES REGARDING AGEING

The study of ageing has expanded rapidly both in depth and in breadth during last two decades. Biological, epidemiological and demographic data have generated a number of theories that attempt to identify a cause or process to explain ageing and its inevitable consequence, death. Many theories have been proposed to explain the process of ageing, but neither of them appears to be fully satisfactory. In this review, we have categorized the various theories of ageing as evolutionary, molecular, cellular, and systemic. Moreover, these theories are not exclusive and may describe some or all features of the normal ageing process alone or in combination with other theories.

Evolutionary Theories:

Evolvability theory is one of the earliest theories on ageing, which was firstly proposed by Weismann and later modified by Mitteldorf [1, 2]. This theory suggests that a purpose of limited lifespan is to save living resources for younger generations. The maximum life span of fruit fly (*Drosophila melanogaster*), laboratory mouse, dog (*Canis familiaris*), man (*Homo sapiens sapiens*) and tortoise (*Testudo*) is around 90 days, 4.5 years, 20 years, 121 years and 150 years respectively. The ageing genes (longevity assurance gene or vitagenes) must be present in all the organisms which determine the rate of ageing and maximum life span. This theory inspired the Mutation Accumulation Theory, which suggests that detrimental, late-acting mutations may accumulate in the population and ultimately lead to pathology and senescence [3].

Cellular Theories:

Theory of mutation:
The weak fitness-selection on old organism allows a wide range of gene mutations in somatic cells, which have deleterious effects on organisms [4]. The mutations gradually get incorporated in DNA by which the corresponding DNA impaired. The impaired DNA may render cell defective in the production of required amount of enzymes resulting in the ageing.

Theory of disposable somatic cells:
Somatic cells are all the cells in the body except gametes and cells involved in gametogenesis. This theory suggests that because of the requirement for reproduction, natural

selection favours a strategy that invests fewer resources in maintenance of somatic cells than are necessary for indefinite survival. Therefore, energy will be spent to ensure minimum damage to molecules such as DNA and to ensure that the animal remains in healthy condition through its natural life expectancy in the wild, where accidents are the predominant cause of death. The theory also presumes that an organism must budget the limited energy available to it, and the energy has to be well distributed and budged for metabolism, reproduction, and maintenance. Insufficient repair is therefore the cause for deleterious changes of body with age [5].

Theory of mitochondrial DNA
This theory suggests that the loss of effectiveness of one of the cell's key organelles paves the way for age-related degenerative diseases. The mitochondria, which are the energy-producing bodies within a cell, have their own genome (Mitochondrial DNA or mtDNA). This mtDNA is synthesized at the inner mitochondrial membrane near the sites of formation of highly reactive oxygen species. mtDNA seems unable to counteract the damage inflicted by these by-products of respiration because, unlike the nuclear genome, it lacks advanced repair mechanisms. Thus, the cell loses its ability to produce energy, and gradually dies.

Theory of nucleotide degeneration:
In ageing cells, the nucleolus is found to degenerate. The SESI (Staphylococcus epidermis surface protein I) gene which helps in the maintenance of the nucleolar structure becomes degenerative.

Theory of DNA Damage/Repair:
DNA damages occur continuously in cells of living organisms. While most of these damages are repaired, some accumulate, as the DNA Polymerases and other repair mechanisms cannot correct defects as fast as they are apparently produced. These accumulated DNA damages probably interfere with RNA transcription. It has been suggested that the decline in the ability of DNA to serve as a template for gene expression is the primary cause of ageing. Most damage comes in the form of oxidative damage, and hence is likely to be a prominent cause of ageing.

Theory of Telomere or cell senescence:
Reduction of cell number is thought to be a cause of ageing. This idea is enhanced by the discovery of telomeres. Telomeres are "caps" on the functional end of chromosomes. The discovery of telomerase provides a support to this theory, because telomerase was found mainly in germ cells and tumor cells [6]. It has been observed that with each cell division the telomeres are shortened by 50-100 base-pairs. The loss of sequence containing important information could cause cellular senescence [7, 8]. The cell strains with shorter telomeres undergo significantly fewer doublings than those with longer telomeres. When the telomeres get too short, the cell stops replicating at an appreciable rate, and so it dies off, which eventually leads to the death of the entire organism. However, studies showed that there is no consistent relationship between telomere-lengths and life spans on animals [9]. In addition, this theory is incompatible with some known facts: **1.** Reduction of cell number is not the unique change of ageing and **2.** Most of organs still produce new cells for repair even in an aged person.

Theory of gene control:
The earliest idea of programmed ageing comes from the observation of planned death on some species. Individuals of female *Octopus* die quickly following reproduction. Hormone signaling has been identified to be the mechanism for programmed death of *Octopus* [10]. Many ageing related genes and life span related genes have been identified [11]; however their exact roles in ageing are still to know completely.

Theory of Gene Regulation:
The theory proposes that senescence results from changes in gene expression. Although it is clear that many genes show changes in expression with age [12]. It is unlikely that selection could act on genes that promote senescence directly. Rather, life span is influenced by the selection of genes that promote longevity. Recently, DNA microarrays have been used to assay genome-wide transcriptional changes with age in several model organisms. Genome-level analysis allows researchers to compile a transcriptional fingerprint of "normal" ageing.

Theory of Reconciliation (on-off switches):
Strehler [13] postulated that the ageing is programmed by the action of 'on-off switches' which resides in the genetic machinery. The mechanism activates first one set of the genes, then other to produce enzyme, hormone or antibody etc. as the individual matures, ages and dies. The specific off switch prevents the key body cells from dividing once the animal has attained maturity.

Theory of gene silencing:
In recent years, SIR (Silent Information regulator) gene is studied. SIR-2 gene homolog from bacteria to human is responsible for the chromatin silencing of NAD-dependent histone deacetylase. There is gradual erosion of silenced chromatin over time that lead to ageing.

Hayflick cellular theory:
Hayflick [7] conducted cell culture experiments following the earlier believe, but demonstrated that in a culture, human fibroblasts multiply for a limited number of generations and then show signs of deterioration, lose their capacity to divide and finally die.

Theory of immunity:
Burnet suggested that thymus gland act as a pace maker for whole body. The thymus gland produces cells that kill and engulf the disease causing bacteria and other microbes. It is primarily based on T-cells, and associated with an increase in susceptibility to infections as well as in incidence of autoimmune phenomena in the elderly. T-cells lose effectiveness in early life due to the decay of the thymus gland. In other words, the quality and quantity of T-cells begins to decline after puberty. Its atrophy is a programmed event and

leads to senescence. Therefore, as one grows older, certain antibodies lose their effectiveness, and fewer new diseases can be combated effectively by the body, which causes cellular stress and eventual death.

Molecular Theories:

Theory of free radical:
According to this theory free radicals are the main origin of ageing by causing oxidative cellular injuries [14]. A free radical is any molecule with one or more unpaired electrons in its valence shell. These small molecules are produced as by-products during some biochemical reactions or as substrates for other biochemical reactions. Free radicals are probably leading to the deterioration of lipids, collagen, elastin and other body substances. Although some studies have shown the effects of anti-free-radical on extending life spans of animals on yeast, *Drosophila*, and roundworms [15], the role of free radicals in ageing is controversial [16].
For ageing, oxygen-based free radicals such as superoxide (O_2^-), hydroxide (OH^-), singlet oxygen (O), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) are of much importance. These substances are also known as Reactive Oxygen Species (ROS). Unfortunately, free radicals cannot be avoided since they are byproducts of essential reactions in the body such as the process of metabolizing oxygen.
Free radicals wreak havoc at a cellular level since they are able to:

- Break off bio-membrane proteins and thereby destroying cellular identity, fuse membrane lipid and proteins, hardening the cell membrane and leading to brittle and nonfunctional cells.
- Disrupt the nuclear membrane. Free radicals may expose genetic material in the nucleus, leaving the DNA open for mutation or destruction.
- Burden the immune system by damaging immune cells.
- Cause chronic diseases.

These effects are known as oxidative stress and may lead to DNA mutations, cell death and disease, all of which contribute to the overall effects of ageing. To prevent oxidative stress, one should reduce environmental burdens in the body (chemicals/heavy metals), reduce stress, improve the quality of one's food supply, and (if possible) increase one's antioxidant mechanisms.
Antioxidants are the body's solution to oxidative stress. These molecules neutralize free radicals by supplying them with extra electrons. This exchange results in lowering the reactivity of the free radical and leaving the antioxidant itself with an unpaired electron. Some important antioxidants are:

- Enzymes such as glutathione peroxidase, catalase and superoxide dismutase.
- Nutrients including vitamins C and E, β-carotene, selenium, cystine, uric acid.
- Synthetic molecules such as DSMO, BHT, and BHA.

Superoxide dismutase destructs superoxide radical and catalyzes following reaction:

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

The molecular oxygen participates in the oxidation of organic compounds:

$$RH + O_2 \rightarrow R^* + HO_2$$

$$R^* + O_2 \rightarrow RO_2$$

$$RO_2 + RH \rightarrow R^* + ROOH$$

$$R^* + R^* \rightarrow R : R$$

This is perhaps one of the well-studied theories, rests on the fact that oxidants induce a variety of distinct biochemical changes in target cells. Hydrogen peroxide is considered one of the more troublesome oxidants, as it diffuses into target cells where site-directed hydroxyl radical formation injures specific targets. DNA is particularly sensitive to hydroxyl radical-induced damage: both DNA strand breakage and base hydroxylation can be detected. The breakage of the DNA strand activates a DNA binding protein [poly (ADP-ribose) polymerase], which forms polymers of ADP-ribose bound to various nuclear proteins using NAD as its substrate. NAD turnover under these circumstances increases so dramatically that it affects ATP synthesis, to the point where high enough concentrations inactivates mitochondrial ATP synthesis.
If the concentration of hydrogen peroxide is high enough, these pathways will lead to cell death and therefore, hydrogen peroxide-induced alterations will not be passed on to future generations. If, however, cells are exposed to sub-lethal concentrations of hydrogen peroxide, the ensuing injury could cause permanent and transmissible cellular alterations which could be biologically detrimental. For instance, if hydroxyl anion-induced DNA damage fails to be repaired or is improperly repaired, this DNA damage could lead to genetic alterations such as mutations, deletions, and rearrangements. Moreover, if these genetic alterations occur in critical genes that are involved in cell growth and differentiation, they could lead to deregulated cell growth and differentiation and ultimately contribute to the malignant transformation of cells. Hence, the growing number of free radical diseases includes the two major causes of death, cancer and arteriosclerosis.

Theory of Advanced Glycosylation Products:
Glucose combines with proteins to form advanced glycosylation products. With advancing age, these products collect, gum up the tissue so that the latter becomes less static with impaired ability to replicate.

Theory of Calorie Restriction:
Caloric restriction is the most potent and reproducible environmental variable capable of extending the life span in a variety of animals from worms to rats. It minimizes glucose entering the cells and decreases ATP generation. Majority of free radicals are emitted during ATP synthesis. Less production of free radical will be there which produce ageing.

Theory of radiation:
This theory is focused primarily on the aging of skin cells, as they are most directly affected by external sources of radiation. Radiation can create free radicals in cells, as the radiation strikes surrounding water molecules and other proximal targets. Experimental studies have recently shown that the shorter, more energetic spectrum of the ultraviolet range is responsible for the dermal connective tissue destruction observed in photo aged skin. Also, it has been shown that ultraviolet and infrared radiation contributes significantly to photo ageing, producing, among other changes, severe elastosis. Thus, even small amounts of radiation are enough to accelerate the aging process, although this theory is, as they say, only skin-deep.

Theory of cross-linkage:
The unpaired electrons establish an increased molecular cross-linking, thereby reducing the functional capacity of the cells. Ageing is caused by the increase in the bonds between protein and nucleic acid. These bonds alter the functional characteristics of cellular components leading to malfunctioning of cells.

Theory of diffusion:
The large molecules may be produced at a rate faster than that at which these can be removed from the cell resulting in their accumulation in the cell cytoplasm.

Theory of metabolism:
It has been observed that animals exhibiting great metabolic rate have shorter life span. It tells that animals that are more active show early signs of ageing.

Systemic Theories:

Developmental theories:
This theory suggests that ageing is a result of development and its process is regulated by the same mechanism as that in development [17]. This idea was supported by the discovery of correlation between the potential of longevity and the mature time of an animal.

Multi-approach Theories:

Theory of Integration:
Integrated system considers that changes in one part of the system drastically affect the operations in other part of the system. The theory believes that cross-linking in all types of molecules both collagenous and non-collagenous is the major factor in ageing.

Theory of Environment-cum-Genetics:
It states that the process of ageing is an outcome of interaction between the genes and environment.

Theory of stress (wear and tear):
Every day stress on the body leads to irreversible damage and finally results in death. Stress-induced senescence occurs in response to a variety of stressors, including DNA damage, modifications in heterochromatin structure and strong mitogenic signals.

Theory of error-catastrophe:
On the basis of recommendations of Orgel [18], it has been concluded that, if error in the reading of genetic code are incorporated in the enzymes required for protein synthesis, will result in further mistakes in the synthesis of structural protein leading to ageing.

Theory of neuro-endocrine system:
This theory proposes that ageing is due to changes in neural and endocrine functions that are crucial for coordinating communication and responsiveness of all body systems. An important component of this theory is the perception of the hypothalamo-pituitary-adrenal axis as the master regulator, the "pacemaker" that signals the onset and termination of each life stage. Ageing produces primary defects in certain centers of brain which control the function of endocrine glands. Such defects cause hormonal imbalance in the body, which in turn disturbs the physiology of body. It is regarded as the brain-endocrine master plan eg, reduced production in the sex hormones in many mammals including men show signs and symptoms of ageing.

Theory of Endocrine Dysfunction:
It is observed that pineal gland growth and puberty onset as well as ageing are programmed and melatonin secretion only delays ageing. Biological clocks act through hormones to control the pace of ageing. This theory has recently been supported by data showing that an "ancestral" insulin pathway controls stress responses and longevity in *Caenorhabditis elegans.* Recent studies confirm that ageing is hormonally regulated and that the evolutionarily conserved insulin/IGF or insulin/insulin-like growth factor-1 signaling pathway plays a key role in the hormonal regulation of ageing.

CONCLUSION

Ageing is an ontogenic issue; the process of growing old and/or the sum of all changes that occur with the passage of time from fertilization to death, but not irreducibly so. Many of the pleiotropic changes that occur with ageing may result from one or more primary changes that affect many downstream processes. This interconnectivity of the ageing process often obfuscates the root cause of ageing and limits the ability to draw definitive conclusions from experimental results. Therefore, it may be concluded that the ultimate causes of ageing remain unknown. On the other hand, a great deal of the ageing process is understood and may only require the integration of various theories to account for normal ageing. The traditional theories are incomplete on interpreting ageing. Evolutionary theories interpret the evolutionary advantage of ageing. However, some theories including cell senescence/telomere theory and gene-controlling theory have unfortunately ignored the influence of damage on ageing. Free-radical theory suggests that free radicals are the main cause of ageing. We can now explore the molecular mechanisms that connect changes in gene expression due to insulin signaling and perhaps calorie

restriction with its ultimate consequence, the delay of aging. An advanced theory is needed, which include all of these useful ideas in traditional theories.

COMPETING INTEREST

The authors have declared that no competing interests exist.

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