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Research Progress on Aging Mechanisms

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Abstract

Aging refers to a gradual process of functional and organic recession with the age increased after the organism maturing. Many researchers have tried to elucidate aging mechanism which includes the free radical theory: free radicals can become lipofuscin and cause the mutations of mitochondrial DNA (mtDNA), and the damage of the nuclear DNA. From the view of heredity, aging is the results of the activation and inhibition of a series of genes as well as the products of their interaction. From the changes of immune function theory, it points out that aging is attributed to the decline of immune responses and the increase of autoimmune reactions.

Keywords

Aging, Free Radical, Lipoprotein, Apoptosis, Mitochondrial DNA, Genes, Immune System

1. Introduction

Aging refers to a gradual process of functional and organic recession with the age increased after the organism maturing, including the decline of the stability of the homeostasis, the decrease of the ability of stress decreased, and the gradual degeneration of structure and components, and finally trend to death [1]. Research on aging has been one of most basic and important parts in life sciences, but the details of the process have been still poorly understood. In the past 20 years, although scientists have made great progress, it is still very limited [2]. Aging is a continuous, dynamic gradual and complex process. The process starts with the end of growing season, which negative impact appears gradually in old age through the system disorders, the decline of organ function, degeneration, and changes in the molecular structure of proteins and enzymes. The main feature is the dysfunctions of organs and tissues and the ability to adapt to environmental stimulus reduced, even lost totally. There are many factors that influence ageing, including social factors, economic, disease, nutrition, heredity factors, lifestyle, environment and mental state, etc. Therefore, the aging is an interaction result of many factors [3]. Nowadays, with the progress of the research of the cellular and molecular biology, the study of aging mechan-

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ism has been from the overall level up to the molecular levels. In recent years, many theories about cells aging have been proposed, such as cell damage, biological macromolecules damage, free radical, and the telomeres theory. For the organism, there are many factors that influence cell ageing, both inherited genetic factors and environmental factors, but the basic cause is the heredity factors.

2. The Features of Cells Aging

Cells aging includes two aspects: the first aspect is that cells proliferation and differentiation will stop finally; and the second aspect is the maintenance of cells basic functions, the stop of growth, but it still maintains the metabolism. The aging cells are polygonal and become bigger, with the nucleus larger, inclusions containing, chromatin aggregation, condensation, fragmentation, dissolution, membrane retraction, cytoplasm vacuolation, mitochondrial number abnormality, Golgi fragmentation, Nissl body disappearance, and membrane fluidity decreased. Many stimuli factors can induce cells aging, including telomere shortening, DNA damage, high oxidative stress, sustained stimulation of mitogen, and other cell stress [4] [5]. telomerase shortening to some extent, can cause the lost of telomere function, and then similar signal of DNA damage is generated, it can be induce aging, but telomere shortening is closely related to cells proliferation, thus this type of aging is known as "replicative aging"; Other factors induce aging rapidly and the telomere length has no change apparently, including overactivation of Mitogen bypass, such as overexpression of Ras, Raf, MEK, E2F, etc. [6]. This type of aging is known as "stress-induced aging". Although research on stress-induced aging mechanism is not so much as replicative aging mechanism, phenotypic characteristics and molecular signals from these two types of aging are very similar.

3. The Mechanism of Cells Aging

Exploring the mechanisms of aging is an ancient and new field of scientific research. With in-depth study, the free radical theory, telomere theory, DNA damage theory, immune theory and other theories have been proposed.

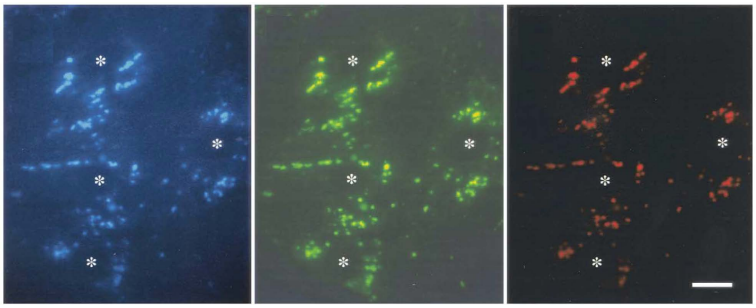
3.1. Free Radical Theory

In 1956, Harmon D puts forward the free radical theory of aging, which pointed out that the major cause of human aging was constantly produce free radicals in cell metabolism processes [7].

Free Radical (RF), also known as free radicals, is the outer orbit of atoms or special status of molecules containing unpaired electrons, because of the natural tendency of electrons in pairs, the unpaired electron has a "tension" to look for "partners". There are superoxide radical ($\bullet O^{-2}$), hydroxyl ion free radical (•OH), hydrogen peroxide free radical (•OOH), hydrogen radical (•H), lipid radical (•L), lipid peroxide radicals (LOO•), organic free radical (R•) and organic peroxide radicals (ROO•) produced during body activity (such as cellular respiration, the process of oxidation in mitochondria) [8]. Free radical plays an important role in the metabolism of human body. All kinds of free radicals will participate in many physiological processes, such as redox reactions of mitochondria and microsome, and the killing effect of leukocytes to pathogens and tumor cells. Under normal condition, free radicals can be cleared by defense system-antioxidant enzymes and antioxidants in vivo, and there is no toxic effect on cells. With the remove of free radical of enzyme that reduces in activity or decreased in number, which can lead to increase of free radical in vivo, and when other factors such as ultraviolet, X-rays, γ-rays, cigarette smoke, oxidants, electronic radiation induce abnormality of the production of free radical, these excessive free radicals will cause damage on protein, DNA, and lipid in human body [9] [10], its free radical-induced mechanism involves following aspects.

3.1.1. The Formation of Lipofuscin

Lipofuscin is an intralysosomal, polymeric substance, and primarily composed of cross-linked protein residues, forming due to iron-catalyzed oxidative processes [11]. It often called age pigment and considered to be a hallmark of aging. This is not only because the amount of lipofuscin increasing with age, showing an almost linear dependence, but also, and more importantly, because the rate of lipofuscin accumulation correlates negatively with life-span. An important property of lipofuscin is its broad autofluorescence. In nonstained morphological specimens, lipofuscin granules can be observed by fluorescence or laser scanning microscopy using excitation lights of different wavelengths in combination with different barrier filters (**Figure 1**) [12].



(a) (b) (c)

Figure 1. Autofluorescence of lipofuscin granules in neonatal rat cardiac myocytes keeps in culture for 3 months. (a), (b), and (c). Luorescent images use ultraviolet (330 - 380 nm), blue (450 - 490 nm) and green (510 - 560 nm) excitation light, and 420, 520, and 590 nm barrier filters, respectively. Asterisks indicate the nuclei. Bar, 10 μM.

Lipofuscin accumulation in brain cells that will be damage the phospholipid membrane, and lead to changes in the sub cellular structure such as the reduction of mitochondria and rough endoplasmic reticulum, it also reduces the number of neurons cells ,and can result in a series of disorders in memory and function of brain, even leads to Alzheimer's disease and other age-related disorders [13]; Lipofuscin accumulation in skin cells that will arouse the formation of age pigment causes collagen polymerization, which lead to the skin without tension and elasticity, wrinkles increase and senile bone proliferation; Lipofuscin accumulation in myocardial cells that will result in cardiac dysfunction [14]. All of the basic characteristics of aging mentions above.

3.1.2. Mutations in mtDNA

Since at the first time of Harman (1972) has proposed the mitochondrial DNA hypothesis, which is closely related with aging. There are a large number of experimental studies have been confirmed this view. Mitochondrial DNA (mtDNA) mutations can be detected in several of degenerative diseases, such as aging and cancer. It increases significantly during aging, especially more prominent in the high oxygen consumption of organizations such as brain and muscle. Because of mtDNA nudity, there is no protection of histone and lack of effective repair system, the thymine, uracil, guanine in mtDNA molecule to react with the function of $\bullet O^{-2}$ and •OH, and then causing of base substitution, reorganization or deletions in mtDNA, resulting in germ-line and somatic cell mtDNA mutation rate than nuclear DNA (nDNA) 10 - 100 times, and being accumulated continuously in the cell. Barja, G [15] points out that ROS (reactive oxygen species) can attack many different cellular macromolecules, including proteins, lipids and DNA. Damage to DNA must be most important for aging, especially in postmitotic cells such as neurons. mtDNA is situated very close to the site of mitochondrial ROS production. Because long-lived vertebrates have low rates of mitochondrial ROS generation, this should affect the level of oxidative damage in their mtDNA (**Figure 2**).

The mtDNA mutations of germ cells-line can cause inherited oxidative phosphorylation (OXPHOS) capacity defects, which lead to degenerative disease occur earlier; The accumulation of mtDNA mutations in somatic cells is closely related to human tissue and organs (brain, heart, skeletal muscle, liver, oocyte and sperm) with aging of body and many age-related degenerative diseases [16]-[18]. Melov detected 35 cases of normal skeletal muscle by PCR, and found that the mtDNA mutation rate of individuals was very low under the age of 40, but a wide range occurred over the age of 50 [19]. From the view of heredity, mtDNA mutation can be divided into two types: point mutations and recombination mutations (deletion mutations and multiplication mutations), both of them can lead to organism reduction, myocardial ischemia, elderly heart failure and other heart diseases. Zhang *et al.* [20] researched on the relationship between age and seven kinds of mtDNA mutations (five kinds of point mutations and two kinds of deletion mutants) through quantitative PCR technique, and found that point mutations appear in the 1-year-old of infant tissues. In the point mutations, the A → G at 3243th locus mutation significantly with age, and other four kinds of point mutations does not increasing, however, for deletion mutation, the detected two deletion mutants (4977 bp and 7436 bp) were significantly increased with age. Many studies have shown that the mtDNA mutations accumulated with age up to a certain threshold value, and can lead to serious obstacles to the supply of cellular energy, and result in decrease of physiological function of tissues and organs.

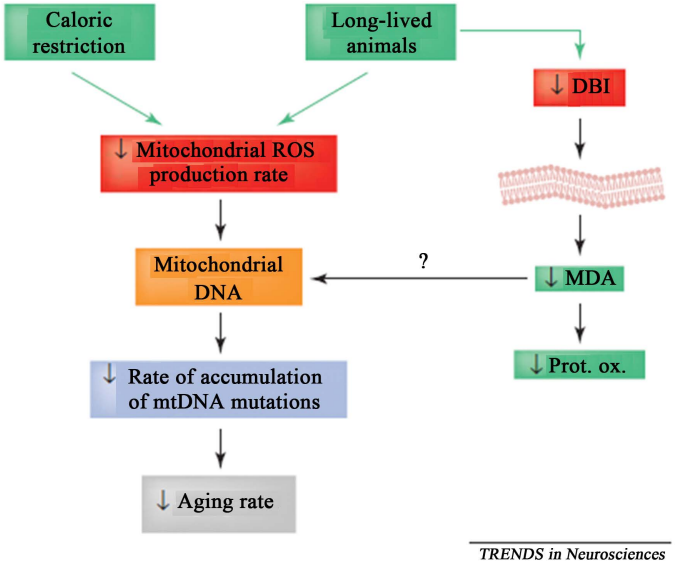


Figure 2. The summary of available results from mammals and birds is related to aging and oxidative stress. Both long-lived and calorie-restricted animals constitutively have low levels of production of mitochondrial reactive oxygen species (ROS), which could be responsible for their low rate of accumulation of mitochondrial DNA (mtDNA) mutations, and thus for their low rate of aging.

3.1.3. Nuclear DNA Damaged

The strong oxidation of free radical arouse nucleic acid oxidized, cross-linked, and results in broken and mutant, which has seriously impact on the normal transcription and translation of genetic information, with the protein expression decreased or even to disappeared, the mutant proteins produced, and the protein synthesis reduced, which is the important reason of the memory impairment, mental retardation and muscle atrophy with age.

4. Telomeres and Telomerase Theory

Telomeres are the chromosomal end of special structure of eukaryotic cell and are related intimately to the cells aging. It consists in many simple sequence repeat (Human beings is TTAGGG) and protein. Telomeres have protected the end of chromosomes to prevent DNA repair from the fusion between chromosome, and from telomeres losing and shortening during DNA replication. It is also the function to maintenance of genome integrity and stability [21]. When DNA replication, small amounts of the end of DNA loses owing to incomplete DNA replication, and the telomeres shorten to an extent after several hundred base of telomere DNA is lost, it cannot maintain the stability of chromosomes, and arouse the cells stop dividing, resulting in ultimately in death, and causing aging [22]. Telomerase is a ribonucleoprotein enzyme that contains primers specific recognition sites, it is own RNA as a template for reverse transcriptase, the telomere DNA synthesis and added to the chromosome ends to make telomere extension, thereby extending the life span of cells even to its immortalization. Calvin B Harley *et al.* [23] studies have shown that the life span was inverse with the telomere shortening speed and in a direct proportion to the telomerase activity and the intrinsic aging processes almost controlled by the accumulation of aging telomere shortening (**Figure 3**).

With the age increasing, the rate of telomere length of epidermis and dermis shows obvious reduction that the average reduction rate was 9 and 11 bp/year [24]. Stewart *et al.* [25] suggested that the main function of telomerase is to extend the length of telomere overhang. Feng *et al.* [26] succeeded in cloning the telomerase gene, which located on chromosome 3 (3q23.3), including the sequence 5'-GUAACCCUZAC-3' complementary to telomere sequences TTAGGG, thus specifically synthesis to telomeres of the human chromosomes. Studies found that the expression of human telomerase catalytic subunit was closely related to telomerase activity [27] [28]. Therefore, the telomere was also known as "life clock" to cells. In 2009, the Nobel Prize in Physiology or Medicine Prize is awarded to Elizabeth Blackburn, Carol-Greider, and Jack Szostak, for their discoveries of the mechanism of telomeres and protecting chromosomes.

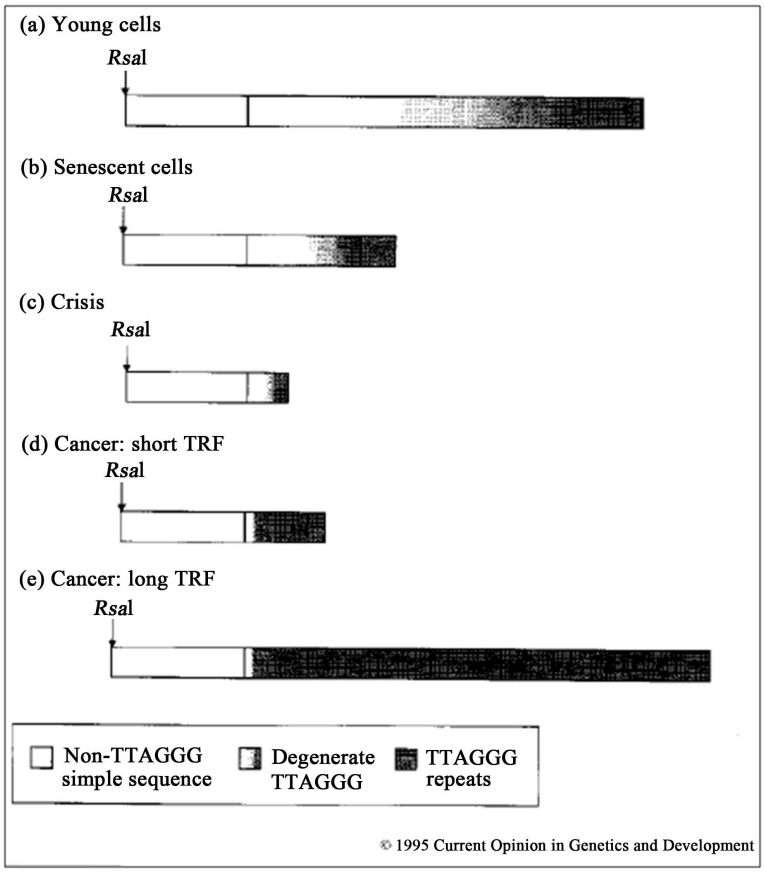


Figure 3. Simplified model of human terminal restriction fragment (TRF) structure. (a) An average TRF in cells from a newborn baby may have −4 - 6 kb of pure]q-AGGG repeats at the terminus and 3 - 5 kb of degenerate TTAGGG repeats and other simple sequence DNA distal to the first restriction enzyme site (e.g. *Rsal*). (b) In senescent cells, most of the pure TTAGGG repeats have been lost, leaving the degenerate TTAGGG repeats and non-telomeric sequence. As non-telomeric repeats do not seed new chromosome ends, it is unlikely that the degeneration of TTAGGG repeats will fully function as telomeres. Assuming some heterogeneity in telomere length between chromosomes, the TTAGGG repeats on at least the end of one chromosome may be of insufficient length for telomere function. Thus, the cell could halt proliferation at senescence because of a critically short telomere. (c) If the cell has mutations or alterations in the cell cycle checkpoint pathway allows senescence to be bypassed, then telomeres would continue to shorten until most of the pure and degenerion of TTAGGG sequence was lost on essentially all chromosomes. At this point, “crisis” occurs, resulting in massive genomic instability and cell death. (d), (e) Rare cells which survive crisis reactivate telomerase and restore telomere function by adding pure TI-AGGG repeats to chromosome ends. Depending on the balance of telomere loss and telomerase activity, telomeres could be short or long.

5. DNA Damage with Aging

DNA damage can be induced mutations that cause cancer or cell death or senescence, contributing to aging. The type of damage that occurs is important for the type of the outcome. Some lesions are primarily mutagenic, others mainly cytotoxic or cytostatic (**Figure 4**) [29].

Under the normal condition, DNA has self-repairable ability that is involved in synthesis and suppression of DNA. The damaged DNA could synthesis and repair after degradation. Both the DNA synthesis inhibitory factor and synthetic promoting factor are exist in aging and normal diploid fibroblasts cells, and to keep relative balance in normal condition, however, this balance is gradually broken with age, and shows cell division slowly or stop due to DNA synthesis blocked. A variety of DNA damage accumulates with age, such as chromosomal translocation, single-strand, double-strand DNA breaks and deletions. The phenomenon of DNA damage is not

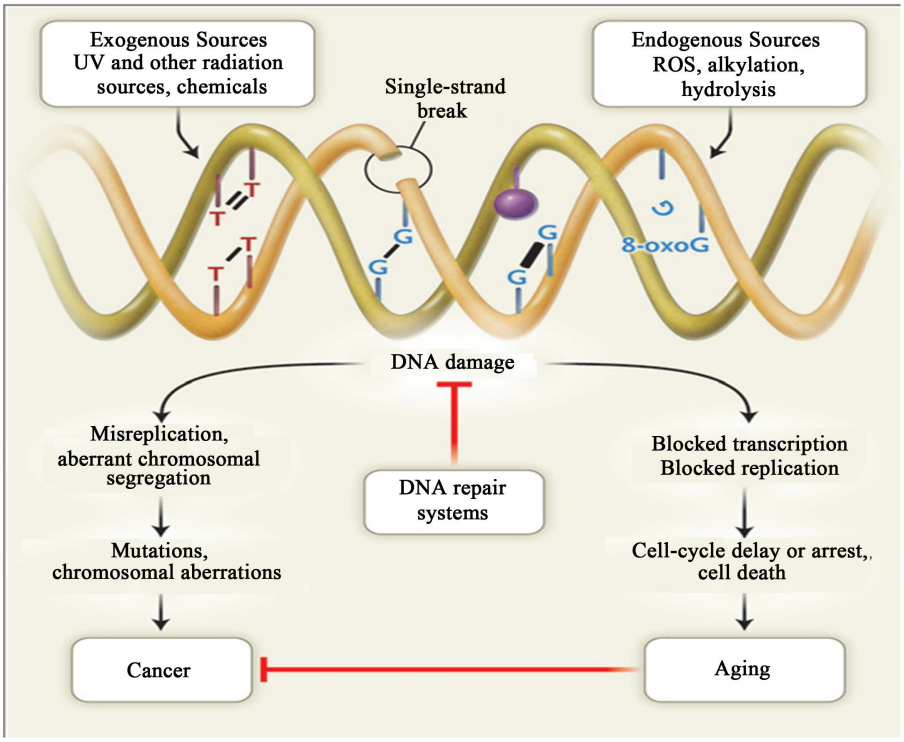


Figure 4. DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), a basic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepairing or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine.

only associated with higher rates of the free radical production in aging process and the antioxidant levels decreases, but also closely related to the reduction of DNA repair capacity. the DNA repair capacity of human blood cells, lymphocytes and skin fibroblasts was reduced with age, some progeria have defects in DNA repair, such as Werner syndrome and Cockayne syndrome, and food restriction can increase DNA repair capacity of rodents, Above results of the experiment show that ability of DNA repair can be regarded as the biological marker of aging [30]. The DNA damage repair function is responsible for surveilling the level of gene DNA; thus facilitating or regulating capacity of DNA damage repair function could delay aging.

6. Theory of the Immune System

In 1988, Meites proposed that immune-neuro-endocrine network plays an important role in the process of aging [31]. Under the aging status of body, excessive apoptosis of spleen lymphocyte could lead to immune response with function decreased, low cytokine levels and immune surveillance decline. Although immune function changes with age, the immune function decline at old age is primarily related to T cells changes [32]. The thymic cells were decreased in old age body, which lead to T cell proliferation decline. In T cell subsets, cytotoxicity T lymphocyte (CTL) immunity activity decreased significantly ,and the same cell scavenging was reduced also, the number of T-helper cells with degradation of the thymus reduced significantly, it is maturation rate also declined with the proliferation activity decreased. Studies found that, the reduction of the function of T cell is closely related to thymus degeneration [33]. With the morphology and function of the thymus changes, the expression of MHC molecules of thymus epithelial cells reduced, which led to the total number of T cells and an-

tigen-specific T cell immune function decreased, and eventually results in the IL-2 reduction, while IL-2 is from T cells which as a significant index for weigh the immune function, the reduction of IL-2 could accelerates the aging process of body [34]. Under the aging state, B cell maturation process is slowed down, mature cycle extended, and isoforms activity decrease in varying degrees, the antibody production ability and the immune response decreased with age as well.

Natural killer cells (NK cells) have directly killed activity to virus-infected cells and tumor cells, whereas viral infections could induce NK cells to produce interferon, which promote NK cytotoxicity, and enhance the redestruction activity of infected cells, however, NK cells decrease in the marrow and spleen with aging. In addition, the metabolic activity of macrophages also decreased. Macrophages is the immune cells that performance non-specific immune effectors in vivo, which plays an important role in various stages of specific immune response, such as swallowed antigens, lymphokines secretion and promoting the proliferation of T and B lymphocytes.

IL-6 is a multifunction cytokine that produced through mononuclear macrophages, T cells and B cells. IL-6 involved in the regulation of the immune response, hematopoiesis, and inflammation. IL6 was originally identified as a B cell differentiation factor, and thus one of the major functions of IL 6 is antibody induction [35]. In aging and many age-related diseases, the abnormal increase of IL-6 levels, which can lead to a series of immune function and endocrine dysfunction, thus promote the aging process of body [36].

7. Conclusion

Aging is a complicated physiological process, which is the result of comprehensive action of many factors. The research progress in aging is limited to one or more factors, and most of them remain in the hypothesis stage. There is no evidence to support it, and it only responds to a part or a side of the aging process mechanism. Only considering all factors (internal and external) that cause aging can we profoundly reveal the essences of aging.

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