Short Communication

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Ageing: The Cellular Basis

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Abstract

Ageing/ Aging is the process of becoming older. Ageing can refer to single cells within an organism which have ceased dividing (cellular senescence) or tothe population of a species (population ageing). Aging occurs due to accumulation of physical, psychological, and social changes in a human being over time. Ageing is one of the risk factors for most human diseases. Approximately two thirds of the 150,000 of total deaths occurring globally per day is due to age related factors. Aging is characterized by a progressive, generalized impairment of function, resulting in an increasing vulnerability to environmental challenge and a growing risk of disease and death. Ageing and mortality started with evolution of sexual reproduction and emergence of the fungal/animal kingdoms approximately a billion years ago. Normal human cells die after about 50 cell divisions known as Hayflick Limit. There are several theories postulated for the cellular mechanism of ageing. They are broadly divided into two main categories: Programmed and Damage-related. Cellular senescence has been attributed to the shortening of telomeres at each cell division. DNA damage theory forms the common basis of both cancer and ageing. Intrinsic causes of DNA damage are the most important drivers of ageing. According to Free radical theory oxidative reaction leads to the formation of molecular species with unpaired electrons which makes them highly reactive known as Free radicals. Ageing affects the various systems of our body. Prevention and delay of ageing can be done by lifestyle modification. The amount of sleep has great impact on mortality. Physical exercises may also increase life expectancy. Avoidance of chronic stress slows loss of telomeres and decreases cortisol levels. Caloric restriction also delays ageing.

Keywords: Ageing; Hayflick Limit; Telomere; Free Radicals; Caloric Restriction.

Introduction

Aging Occurs due to accumulation of physical, psychological, and social changes in a human being over time [1]. Ageing is one of the risk factors for most human diseases. Approximately two thirds of the 150,000 of total deaths occurring globally per day is due to age related factors [2]. Aging is characterized by a progressive, generalized impairment of function, resulting in an increasing vulnerability to environmental challenge and a growing risk of disease and death [3]. Ageing and mortality started with evolution of sexual reproduction and emergence of the fungal/animal kingdoms approximately a billion years ago [4]. Normal human cells die after about 50 cell divisions known as Hayflick Limit [5].

Biological Basis of Ageing

There are several theories postulated for the cellular mechanism of ageing. They are broadly divided into two main categories: Programmed and Damage-related [6]. Programmed factors follow a biological timetable, perhaps that might be a continuation of the one that regulates childhood growth and development. This regulation would depend on changes in gene expression that affect the systems responsible for maintenance, repair and defence responses [7].

Damage-related factors include internal and environmental assaults to living organisms that induce cumulative damage at various levels [7].

Three main metabolic pathways influence the rate of ageing [8]:

1. The Forkhead box O3 (FOXO3)/Sirtuin pathway.
2. Growth hormone/Insulin-like growth factor-1 (IGF-1) signalling pathway.
3. Electron transport chain in mitochondria.

Most of these pathways affect ageing separately. Targeting them simultaneously leads to additive increases in lifespan [9].

Programmed Theories

1. DNA methylation theory
2. Telomere theory
3. Variation in the gene FOXO3
4. Mechanistic Target of Rapamycin (mTOR) theory
5. Growth hormone/Insulin-like Growth Factor 1 signalling theory
6. Evolutionary theories of ageing
7. Reproductive-cell cycle theory
8. Autoimmunity theory
9. Energy homeostasis theory

Horvath hypothesised that DNA methylation age measures the cumulative effect of an epigenetic maintenance system.Prematurely aged mice can be rejuvenated and their lives extended by 30% by partially "resetting" the methylation pattern in their cells by activating the four DNA transcription factors – Sox2, Oct4, Klf4 and c-Myc [10].

Cellular senescence has been attributed to the shortening of telomeres at each cell division. When telomeres become too short, the cells senesce and die or cease multiplying. The length of telomeres is therefore the "molecular clock". The telomeres are protected by telomerase enzyme. Oxidative stress, has an bigger effect onthe rate of telomere loss and telomere shortening [11,12].

Variation in the Forkhead box O_3 ($FOXO_3$) gene has a positive effect on the life expectancy of humans and found in people living to 100 and beyond. Acts on the sirtuin (SIRT) family of genes which also have a significant effect on lifespan. Sirtuin in turn inhibits Mechanistic Target of Rapamycin (mTOR) [13].

Mechanistic Target of Rapamycin (mTOR) is a protein that inhibits autophagy has been linked to ageing through the insulin signalling pathway. When organisms restrict their diet, mTOR activity is reduced, which allows an increased level of autophagy. This recycles old or damaged cell parts, which increases longevity. mTOR inhibition and autophagy reduce the effects of reactive oxygen species on the body [14].

The studies showed that decreasedGrowth hormone/Insulin-like Growth Factor 1 signalling theory increased longevity [14].

Evolutionary theories of ageing states that antagonistic pleiotropy gene has a double function – promoting growth and development early in life to achieve reproduction, but becoming dysregulated later in life, driving senescence. Ageing is regulated by reproductive hormones that act in an antagonistic pleiotropic manner via cell cycle signalling [15].

According to autoimmune theory ageing results from an increase in auto-antibodies that attack the body's tissues. A number of diseases are associated with ageing, such as atrophic gastritis and Hashimoto's thyroiditis [16].

Energy homeostasis theory states that the imbalance between cellular energy generation and consumption promotes ageing process. Thus tight regulation of balance between cellular energy generation and consumption is required to delay ageing. It was demonstrated that acetylation levels of AMP-activated protein kinase slows ageing [17].

Damage related theories

1. DNA damage theory
2. Genetic theory
3. Accumulation of waste theory
4. Wear and tear theory
5. Mitochondrial theory
6. Free radical theory

DNA damage theory forms the common basis of both cancer and ageing. Intrinsic causes of DNA damage are the most important drivers of ageing such as Genetic damage (aberrant structural alterations of the DNA), Mutations (changes in the DNA sequence), and Epimutations (methylation of gene promoter regions) [18,19,20]. These cause abnormal gene expression. DNA damage causes the cells to stop dividing [21].

Genetic theory states that rate of aging varies between species but not much within species due to difference in genetic programming.Aging cannot

be prevented even under best of circumstances. Gradual impairment of function is genetically programmed [22].

Accumulation of waste theory suggests that buildup of waste products in cells interferes with metabolism. A waste product called lipofuscin is formed by a complex reaction in cells that binds fat to proteins. Lipofuscin accumulates in the cells as small granules, which increase in size as a person ages [23]. Autophagy enhance clearance of toxic intracellular waste thus improving lifespan [24,25].

Wear and tear theory is concerned with the changes associated with ageing are the result of chance damage that accumulates over time.Ageing also results from chance events that escape proof reading mechanisms, which gradually damages the genetic code [26].

In Mitochondrial theory, mtDNA mutations lead to respiratory-chain-deficient cells and thence to apoptosis and cell loss leading to increased generation of reactive oxygen species (ROS) [27].

According to Free radical theory oxidative reaction lead to the formation of molecular species with unpaired electrons which makes them highly reactive known as free radicals- superoxide, hydroxyl radicals [28]. Free radicals damagevital macromolecules such as DNA and Proteins. Membranes of cells and organelles are also damaged by lipid peroxidation.Antioxidants such as Glutathione, Vit. A, C, E can be usedto prevent such effects [29].

Network theory is a newer concept that takes into consideration the interaction and synergism between different theories.Understanding these connections is likely to be important in developing effective interventions against age related cellular deterioration [30].

Age Related Changes

In hematpoietic system marrow is replaced by fatty marrow. Physiological reserve capacity for erythropoieses is reduced. There is decline in immuno- competence thus increased suceptibiltyto infection and also increase in auto- reactivity to autoimmune diseases [31].

There is decline in respiratory function due to structural and functional changes.Alveoli becomes flatter and shallower, wall gets thinner and contains few capillaries leading to reduction in pulmonary diffusing capacity. Total and timed vital capacity decrease and increase in residual volume. Loss of elastic recoil of lungs thus leading to overall impairment of ventilation, diffusion as well as regulation [31].

In Cardiovascular system atherosclerosis is extremely common in elderly. Elasticity of aorta and other large arteries decreases with increasing age, as a result systolic and pulse pressure are increased. Myocardium shows atrophy accompanied by deposition of a brown pigment lipofuscin. Structural changes in the valves are seen. There is reduction in number of pacemaker cells [31].

The alimentary canal: Teeth show attrition. Weakness of pharyngeal musculature causes dysphagia. Stomach and pancreatic secretions are decreased. There is decreased villus height leading to reduced absorptive surface area. Liver shows decrease in number and increase in size of hepatocytes and fibrous tissue leading todecrease in synthetic function of liver [31].

Excretory system is characterised by reduction in number and size of nephrons.There is ten percent reduction in renal plasma flow per decade after the age of 30 years. Both secretory and reabsorptive functions of renal tubule also decrease [31].

Nervous system suffers dementia whichbecomes more common with age. There is mild cognitive impairment. Progression of neurodegenerative diseases such as Alzheimer's disease, cerebrovascular disease and Parkinson's disease increases [32].

In Reproductive systemfemale fertility declines.Menopause typically occurs between 49 and 52 years of age [33].

Prevention and Delay

Lifestyle modification can be done by taking proper amount of sleep as sleep has great impact on mortality [34,35]. Physical exercise may increase life expectancy [36]. Avoidance of chronic stress slows loss of telomeres and decrease cortisol levels [37,38]. Caloric restriction also plays an important role in prolongation of life [39].

Conclusion

Thus aging is accumulation of physical, psychological, and social changes in a human being over time. According to studies phenomenon of aging occur when pro-aging factors are superseded by anti-aging factors. This may be program related

or damage related. Process of aging can be prevented by modification of lifestyle and caloric restriction.

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