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Science of Ageing: Causes, Effects and Treatments

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ABSTRACT

Ageing, as per the current understanding, may be considered as the accumulation of various molecules as well as cellular damage over time which results in a very complicated physiological process is poorly understood. Ageing leads to a gradual decrease in the physical and mental capacity with an increased risk of disease and death. Researchers have proposed various hypotheses like free radical theory, telomerase theory, wear-and-tear theory, etc. in order to explain these inexplicable phenomena which are also influenced by environmental factors, radiation and lifestyle. The human yearning for longevity has led to the development of various treatment methods including manipulation of a metabolic pathway, the use of antioxidant drugs to prevent oxidation due to free radicals, telomere-based therapy, hormonal therapy using peptide hormone, usage of Anti-ageing compounds, vitamins (e.g. ALT 711), and change in lifestyle, etc. Presently, research on ageing includes investigations into novel methods to reverse ageing and genetic approaches to increase the lifespan as a longer lifespan

contribute to not only the wellness of an individual, but also that of the society as a whole.

Keywords: Ageing, Free radicals, Antioxidants, Telomere, Longevity, Reverse ageing

Biologically, ageing is described as an accumulation of a wide variety of molecular and cellular damage, in an organism over time. This involves a very complicated physiological process which is poorly understood. Scientific research has brought up many different theories that try to comprehensively explain ageing, but none of these explain all the aspects of this biological process. Ageing may lead to a gradual decrease in physical and mental capacity, an increased risk of diseases, and ultimately, death. But these changes are neither linear nor consistent and are only vaguely associated with a person's age in years while also depending on various factors such as lifestyle and environment. As a result, individuals in their advanced years may exhibit good health while those who are younger and expected to be healthier owing to their age may become frail (WHO 2015). Among the different theories formulated to explain the phenomena that constitute ageing, one of the most known and widely studied is the free radical theory of ageing (Harman D. 1956). There is evidence that suggests that ageing may also be associated with epigenetic changes (López-Otín C., *et al.,* 2013). In the last few years, widespread efforts are being made to catalogue the cellular and molecular hallmarks of ageing as well as the interconnection between them. Herein, we are attempting to give a comprehensive overview on how the combination of different epigenetic alterations and oxidative stress affects the process of ageing and the advanced therapies that have been developed in order to be used to delay ageing (Guillaumet-Adkins, A., *et al.*, 2017).

Causes of Ageing

Free Radicals and Ageing

Free radicals are reactive chemical species that have a single unpaired electron on the external orbital (Riley P.A., 1994). The theory of free radicals (Sohal and Weindruch 1996), originally described by Denham Harman in the 1950s proposes that organisms

age because of the accumulation of free radicals (Harman D. 1956), that end up causing cellular toxicity and damage to the nuclear DNA, cellular membrane structures and mitochondrial DNA (mt DNA). This theory also suggests Reactive Oxygen Species (ROS)as the major cause of this oxidative damage, but not the only cause. ROS is a by-product in the cells of most aerobes that is generated either exogenously or endogenously. Exogenously it is produced during UV light irradiation by X-rays and gamma rays or produced during metal-catalysed reactions or may be present in the atmosphere as pollutants. Endogenously these are produced by neutrophils and macrophages during inflammation, and are by-products of different mitochondrial reactions (Inoue M., *et al.,* 2003) or various other mechanisms (Cadenas E.,1989). But several other reports contradict this idea by saying that many forms of damage serve as causal factors in the ageing process. Also, it fails to explain why cells are unable to maintain a balance between damage generation and their removal. Oxidative stress produced by free radicals increases with age which eventually weakens the natural repair systems in older individuals (Kowald and Kirkwood,2000) and is a major contributor to many cardiovascular and neuro degenerative diseases (Ames BN., *et al.*, 1993).

Telomerase

Chromosomes have a specific repetitive sequence at their ends, known as telomeres which are shortened after each cell division cycle. This shortening eventually leads the chromosomes to stop dividing and die. But in some specific cells like the stem-cells, the enzyme telomerase prevents this decline by lengtheningthe telomere. Variations in a gene known as TERC (Telomerase RNA component)have been associated with reduced telomere length (Arvind, and Grace,2018). According to a study, individuals with TERC variations are believed to look several years older when compared to a non-carrier of the same age. (Jae-Hong Kim, *et al.,* 2011) After engineering mice whichlack telomerase, researchers have managed to prove that short telomeres and mutation of the telomerase enzyme may lead to premature ageing as the transgenic mice suffered from infertility and other age-related conditions such as osteoporosis, diabetes and neuro degeneration (Ibid.).

Environmental Factors

Ageing is also known to be affected by environmental factors apart from genetic and/or epigenetic mechanisms (Robert, and Fulop, 2014).

1. *Radiation:* In many species like mice, rats, hamsters, guinea pigs, and dogs, ionizing radiation like X-rays can cause a significant shortening of lifespan. In a study, it was found that small daily doses of continuous irradiation throughout life helps in speeding up the process of mortality. Recent cell-culture studies also show that ionizing radiation leads to more chromosomal aberration which ultimately fastens the mortality process. Natural radioactive potassium, radium and natural background radiation from Earth can cause a small percentage of cancer but are not major contributors of ageing.
2. *Temperature:* Flour beetles, fruit flies, fishes and other poikilothermslive longer because of lower environmental temperature. According to the rate of living hypothesis, an organism's lifespan is dependent on some critical substance that is exhausted more rapidly in high temperature but this was found to be inadequate when a study was done using *Drosophila* spp. by rearing at one temperature for one part of their life and another temperature for the rest of their life. It was also observed that the number of calories expended by fruit flies per lifetime wasmaximumat an intermediate temperature, so the rate of ageing per calorie was minimal at that temperature. Researchers say that the lowering of core body temperature may make humans live longer. In short-lived species, high metabolism increases core temperature which shortens their lifespan. This was tested in engineered mice and the results found that even a 0.5? reduction in temperature can increase the life span by almost 20 per cent.
3. *Environment, infectious disease and nutrition:* Those who live in a poor environment have higher susceptibility rates for infectious diseases and also may suffer from poor nutrition which can speed up the process of ageing. Experiments with rats have shown that

rats on restrictive diets lived longer than those allowed to consume unrestrictedly.

Besides these, many theories regarding the cause and effect of those particular causes have been proposed. Some of them are discussed in the table below:

Table 1
Theories on Ageing

Theory on Ageing	What it Says?
Genetic Theory	Genes of the organism contains factors that specifically determine its lifespan; i.e. the number of repeats in a telomere determines the maximum life span of a cell.
Non-genetic Theories	
1. Wear-and-tear Theory	Accumulation of waste products within cells wear them out by interfering with the function. E.g.-age pigment accumulation in heart, nerve and muscle cells
2. Cross-linking theory	Cross-linking between molecules alter the structure and shape of the molecules making them unable to carry out the function of the cell. E.g. – cross-linking of collagen leads to loss of elasticity.
3. Autoimmune theory	Immune reactions cannot distinguish between self and foreign and start attacking own cells.
4. Glycation theory	Simple sugars like glucose bind to molecules such as proteins and lipids showing a cumulative effect which may lead to shorter life span.
5. Oxidative damage theory	Gradual accumulation of oxidative damage to macromolecules reduces the physiologic functions and is associated with the life expectancy. E.g. – electrons leaking from ETC produce ROS and damage protein.
6. Psych sociological theory	As people grow older, their behaviour, social interactions and the activities in which they engage change.

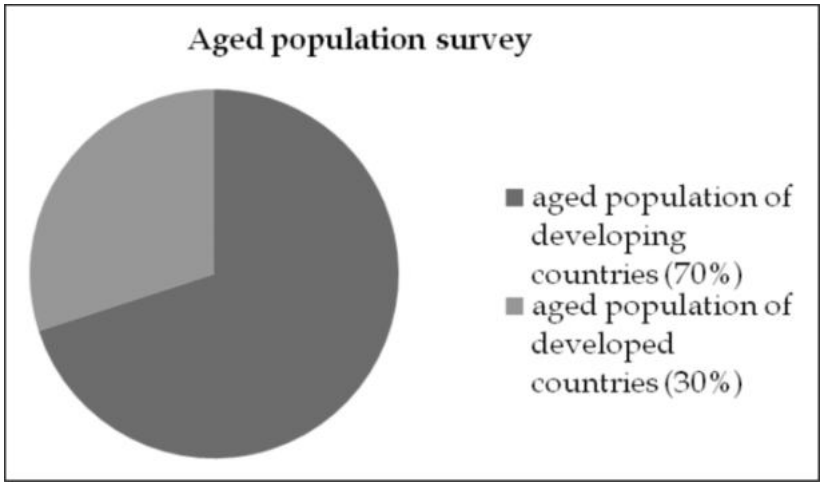
Effect

Ageing comes with several physiological and anatomical changes like nervous dysfunction, decreased cognitive function and memory loss. The function of sense organs like vision, smell, taste and hearing capacity also decreases with some changes. The limb muscles in older people are shorter by at least 25–35 per cent from young adults. After the forties, humans start losing some of the cells in their internal organs. Surveys conducted across age groups also indicate a loss of

height of 1.5 inches per ten years can occur after the forties which become more prevalent past the seventies. Men start losing weight after the age of 55 while women start losing their weight after 67–69 years. Lean muscle tissues are replaced by fat cells in older people. While ageing, the post genetic mechanisms produce a slow-down of most vital functions, of which nervous conductivity declines the slowest and elastic recoil declines the fastest (Shilpa, *et al.*, 2018). One of the most known consequences of ageing is a decrease in the immune response and higher susceptibility to disease.

Figure 1

Chart showing the distribution of aged population across the Globe



Longevity

Most of the research on anti-ageing treatment concentrates on the possibilities involved in the manipulation of the metabolic pathways that are implicated in the progressive decline of biological functions associated with senescence.

Life expectancy cannot be exclusively genetically determined which could be understood from the study of identical twins raised apart. In spite of having identical genomes, they passed away at different ages due to various factors (Segal NL., 2012).

Some of the therapies that may come to the rescue to delay ageing are discussed further.

Free Radicals and Antioxidants

A healthy body requires a balance between free radicals, antioxidants and cofactors. Free radicals induce oxidative stress, which is balanced by the body's endogenous antioxidant systems with the help of co-factors; if the level of free radicals increased and can't be managed by endogenous antioxidant and co-factors, then it can result in rapid ageing and subsequent progression of age-dependent diseases such as cardiovascular disease, cancer, neurodegenerative disorders, and other chronic disorders. To accelerate the function of endogenous antioxidants, antioxidant drugs could be supplied. Most commonly used antioxidants are retinols (Vitamin A) that stimulate the growth of new collagen and combat skin ageing. Selenium and Resveratrol (found in grape skin) arealso used to treat cancer and obesity (Rahman, K. 2007). It is also seen that when the mitochondria were removed, mitochondrial ROS molecules that cause inflammation were reduced to some extent. Interventions like Calorie restrictions, exercise and drugs, such as polyphenols, antioxidants, metformin, ω–3 fatty acids, aspirin, and senolytics specifically target mitochondria and thereby successfully act towards the reversal of age-related damages to an extent.

Telomere-Based Therapies

The telomeres will gradually shorten with time and cell division unless there is sufficient telomerase activity to maintain telomere length. The length of the telomere is maintained by the enzyme telomerase which succeeds in dealing with cellular senescence by lengthening the telomeres. Many companies are developing telomerase–based therapies to fight against ageing. One of the products available is a telomerase activator named TA–65. There has been observational and research studies in animal models and humans that paved way for the development of biomarkers of ageing such as immune, metabolic, bone, cardiovascular, and inflammatory markers, in the absence of remarkable signs of toxicity. The TA–65 can extend telomeres and potentially enhance health outcomes in humans, without any observation or safety concerns (Harley, *et al*., 2011).

Researchers from Stanford University School of Medicine in California have discovered a way to increase the length of human telomeres by around 1,000 nucleotides – around 10 per cent – in a matter of days which can be proper solution hence proceeding to slow and successful ageing. According to some other research, telomere length can be extended by taking Mediterranean diet which is typically high in vegetables, fruits, nuts and olive oil, but low in saturated fats, dairy, meat and poultry and by reducing the amount of sitting time.

Calorie Restriction

Calorie restriction (CR) holds the greatest potential to delay human ageing. Many studies havefound that atherosclerosis can be reduced by the protective effect of CR (7). CR has a protective effect on cardiac function (Meyer, *et al*., 2006), and even has benefits in adiposity to help reducing weight (Racette, *et al.,* 2006). Improved memory in elder people is seen due to CR (Witte, *et al.,* 2009). In overweight people, some biomarkers of longevity are present where CR appears to have beneficial effects (Heilbronn, *et al*., 2006). Calorie restriction can also activate sirtuins gene in different organism, i.e. Sir 2 in yeast, SIRT 1 in humans. In nematodes and fruit fly sirtuinsfunction as anti-ageing genes. In yeast, it regulates a large segment of the chromosome. It suppresses the activity of the genes whose mutation can cause ageing which are also observed in mammals. So the development of drugs that mimic the effect of calorie restriction on the sirtuin gene in humans can help in treating different age-related diseases.

Stem Cell-based Therapy

The stem cells with its self-renewal property have a major role in tissue-life prolongation such that a decrease in stem cell is often associated with ageing. The intravenous or local administration of adult adipose-derived stem cell can be used as an efficient tool in anti-ageing treatment. This is either due to its subsequent ability to differentiate into various cell lines (variable differentiation) by paracrine activity or immune privilege. The in vitro modification and subsequent introduction of stem cells is a novel strategy for rejuvenation of older or deceased cells. The use of induced pluripotent cells to replace cells of organs lacking stem cells is also a novel method of

anti-ageing therapy as it can retain the ability of embryonic stem cells to play a key role in organogenesis and mitigating ageing effect (Jae-Hong Kim, *et al.*, 2011; Yeh, and Chan, 2018; Godic, A., 2019).

Hormonal Therapies

Human growth hormone (HGH) injection is an anti-ageing treatment which is helpful for certain aged group due to its beneficial effects (Besson *et al*., 2003). Another hormone named Insulin-like growth factor 1 (IGF–1) is helpful in ageing as low levels of this hormone seem to correlate with longevity. (Krzisnik, *et al*., 1999). Melatonin hormone that is usually involved in circadian rhythms and sleep, is also associated with ageing and life-extension (Froy, and Miskin, 2007; Kondratov, R.V. 2007). Even Dehydroepiandrosterone (DHEA) makes progress in the health of the elderly by various ways such as enhanced memory, muscle mass, sexual appetite, immune system, and benefits to the skin (Nair, *et al.,* 2006) Oestrogen is also used asa therapeutic agent that helps in anti-ageing . (Dominguez, *et al*., 2009).

Hyperbaric Oxygen Therapy

All the tissues need an adequate supply of oxygen to function. In aged condition, when a tissue is injured, it requires even more oxygen to survive. Hyperbaric oxygen therapy involves breathing pure oxygen in a pressurized form that is three times more than the normal air pressure. It increases the amount of oxygen taken by the blood. An increase in blood oxygen somewhat restores normal levels of blood gases and tissue function to promote healing and fight infection (Carney, AY., 2013).

Vitamin Supplements and Anti-ageing Drugs

Many products that are promoted commercially as having anti-ageing properties include diets, drugs and supplements. E.g.-Vitamin B3 regulates apoptosis and proliferation in the testis of D-Galactose induced aged rat model. A compound called Rapamycin (sirolimus) can increase the lifespan of adult mice by 14 per cent and young mice by 28 per cent. It is an immunosuppressing agent which is also helpful in tissue transplant rejection and also used as an anticancer agent as it can inhibit the proliferation of particular types of cancer

cells. Anotheranti-ageingcompound ALT–711 appears to be helpful against cardiac diseases and can treat ageing as a whole. There are some other genes responsible for ageing which can also be useful for further pharmaceutical intervention and the attempts have been already started, to analyse these genes and could help extend lifespan (Yeh, and Chan,2018). It also shows that ageing can be slowed down naturally through regular exercise.

Successful Ageing

It has been pointed out that successful ageing refers to key ideas such as life satisfaction, longevity, freedom from disability, mastery and growth, active engagement with life and independence (Moody, 2005) in a study that has been reported regarding the association between the inflammatory potential of nutrition and successful ageing in a sample of older adults living in the Mediterranean basin (Sohal, and Weindruch, 1996). Data analysis revealed that the diet high in anti-inflammatory agents (fruits, vegetables, whole grains, etc.) lead to successful ageing. The role of a healthy diet in ageing and longevity has been well clarified in the past (Keys A *et al.,*1984; Mathers JC., 2013). According to meta-data analysis, participants with high NAI score with pro-inflammatory nutrition had a higher chance of hyper cholesterolemia and lower successful ageing (Sohal, and Weindruch, 1996).

Reversible Ageing

De-Pinho's team engineered a mouse where they found telomerase could be switched back on by feeding the mice with a chemical 4-OHT. After a month they were surprised by seeing the result that shrivelled testes grew back to normal and the animals regained their fertility and also other organs, such as the spleen, liver and intestines, recuperated from their degenerated state. Even ageing of the brain was also reversed. Mice with restored telomerase activity had noticeably larger brains and neural-progenitor cells started working again. But there exists a contradictory report regarding this idea when David Harrison said that telomere rejuvenation is potentially dangerous as it can also stimulate cancer. Hence, ethical questions on how to safely use this strategy to reverse ageing remain unanswered (JaskelioffM., *et al.,* 2011).

Reversible Brain Ageing

The progressive loss of dendritic arbours and impairments to synaptic plasticity causes brain ageing. This brain ageing can mostly be reversed bylong-term, oral administration of a positive allosteric modulator of AMPA-type glutamate receptors which is experimented in rat brain. In order to illuminate on how brain softness and stiffness may influence cell behaviour, a group of researchers from the University of Cambridge investigated a cell surface protein, Piezo1—which informs the cell whether the surrounding environment is soft or stiff. When they grew young, functioning rat brain stem cells on the stiff material, the cells became dysfunctional and lost their ability to regenerate and started functioning like aged cells. But when the old brain cells were grown on the soft material, they began to function like young cells which mean they were rejuvenated. Upon removing Piezo1 from the surface of aged brain stem cells, they managed to trick the cells into perceiving a soft surrounding environment, even when they were growing on the stiff material. This led to the conclusion that deleting Piezo1 in the oligodendrocyte progenitor cells (OPCs) within the aged rat brains could lead the cells to become rejuvenated and get back their normal regenerative function (Segel M., *et al*., 2018).

Conclusion

According to the survey result of world population prospects (1950–2050), the number of aged people is increasing more in developing countries than the developed countries. If this continues then, within a few years the aged population count will be 70 per cent from only developing countries which will merely exceed 470 million which is double of the aged population in developed countries (Amarya, S., *et al*., 2018) (Figure 1).

A longer life brings with it opportunities, not only for themselves and their families but also for society. An extended healthy lifespan means individuals can contribute more to society in socioeconomic as well as cultural aspects thus helping in the cultivation of a better society. Older people also can contribute in many ways to their families and communities by utilising their lived experience. Health is

the major factor on which these opportunities and contributions can depend on (WHO 2015).

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