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# Chapter 3: Unraveling the causes of aging: From cells to lifestyle

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**Abstract**

Aging is a natural and progressive biological process influenced by a combination of genetic, molecular, and environmental factors. The primary causes of aging include cellular and molecular damage accumulated over time, genomic instability, telomere shortening, epigenetic alterations, and oxidative stress. Additionally, dysfunctions in mitochondria, impaired protein maintenance (proteostasis), chronic low-grade inflammation, and the exhaustion of stem cells contribute significantly to the decline in physiological functions. Both intrinsic mechanisms, such as programmed cellular responses, and extrinsic factors, like lifestyle choices and environmental exposures, interplay to drive the aging process. Understanding the underlying causes of aging is crucial for developing interventions aimed at extending healthy lifespan and preventing age-related diseases.

**Keywords:** Cell Exhaustion, Cellular Damage, Genetic Factors, Life Style, Food habit, Oxidative Stress, Proteostasis Loss, Stem Environmental Stressors, Telomere Shortening.

## 3.1. Introduction

Aging is a complex process influenced by a mix of genetic, environmental, and lifestyle factors. Scientists have proposed several biological causes of aging, and many of them are interconnected. The main causes of aging are often referred to as the "hallmarks of aging" in modern biology include 1. Genomic Instability: DNA damage accumulates over time from internal factors (like metabolism) and external ones (like

UV radiation, pollution). This weakens the cell's ability to function and replicate correctly, 2. Telomere Shortening: Telomeres are protective caps at the ends of chromosomes. Each time a cell divides, telomeres shorten. Eventually, they become too short to protect the DNA, leading to cellular aging or death, 3. Epigenetic Alterations: Epigenetic changes affect how genes are expressed without altering the DNA sequence. Over time, these changes can disrupt normal cellular function and contribute to aging, 4. Loss of Proteostasis: Proteostasis refers to the balance of protein production, folding, and degradation. As we age, misfolded or damaged proteins accumulate, leading to diseases like Alzheimer's and Parkinson's, 5. Mitochondrial Dysfunction: Mitochondria are the powerhouses of the cell.

With age, they produce less energy and more harmful free radicals (reactive oxygen species), which damage cells and tissues, 6. Cellular Senescence: Cells can enter a state where they stop dividing but don't die. These "senescent" cells secrete harmful molecules that can cause inflammation and damage nearby cells, 7. Stem Cell Exhaustion: Our body relies on stem cells to repair and regenerate tissues. As we age, stem cells lose their ability to renew and function, leading to tissue degeneration and 8. Altered Intercellular Communication: Aging changes how cells talk to each other. Chronic inflammation ("inflammaging") and disrupted signals can impair tissue repair and immune response. Several other factors that contribute for aging process are discussed.

**3.2. Factors affecting ageing process**

In modern ageing theory, the "rate of living" is defined by loss of metabolic activity rather than the loss of vital living activity although advances in ageing research continue to defy this theory. The fiction in modern "rate of living" theory still debate whether "metabolic rate" or "metabolic stability" is considered to be the determinant factor in longevity. To simplify the status on the definition of ageing, Lo´pez-Otı´n et al. (2013) have given nine cellular and molecular hallmarks for it. They are genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication.

Interestingly, all of the above factors found to have some connection as either "cause" or "effects" of OS associated genetic imbalance and ageing in animals (Halliwell and Gutteridge, 2010). For example, Missios et al. (2014) have reported that telomere dysfunction enhances the requirement of glucose substitution (medicate trycarboxylic acid cycle, electron transport chain, oxidative phosphorylation and thus modulates OS pathways, Paital and Chainy 2012, 2014) for the maintenance of energy homeostasis (linked to oxidative phosphorylation) and IGF-1/mTOR-

dependent mitochondrial (act as hub for ROS generation and OS modulation, Paital and Samanta, 2013) biogenesis in ageing tissues.

### 3.3. Causes of ageing

#### 3.3.1 Senescence

Irreversible arrest of cell proliferation is referred as cell senescence. Senescence is the key hallmark of normal cell; conversely cancerous cells undergo uncontrolled infinite cell division (Collado at al., 2007; Childs et al., 2017). However, accumulation of senescent cells plays crucial role in ageing and age-related disorder including cancer (Zeng et al., 2018), neurodegenerative disorders such as Alzheimer's and Parkinson's (Bitto et al., 2010; Salminen et al., 2011), cardiovascular diseases (Shimizu and Minamino, 2019), COPD (Mercado et al., 2015), macular degeneration, emphysema (Regulski, 2017), etc. Cell senescence is multifactor, multifaceted and multi-mechanistic process, several factors are responsible for driving a normal dividing cell to attain senescence (Hernandez-Segura et al., 2018). The ends of eukaryotic chromosomes are made of repetitive DNA-protein complex called as telomeres. Telomeres act as buffer against DNA damage that might occur during the replication of linear chromosomes (Muñoz-Espín and Serrano, 2014).

Telomerase; a eukaryotic RNA-dependent DNA polymerase plays a striking role in synthesizing telomeric repetitive DNA sequences (Siderakis and Tarsounas, 2007). Elevated levels of telomerase expression and activity are observed in fertilized egg, and most of the cells present in somatic tissue at 16-20 week embryonic development. As tissue differentiation progress extinction of telomerase activity is observed in most somatic cells except certain types of stem cells, male germ cells, and activated lymphocytes (Aravinthan, 2015; Xie et al,. 2015). In absence of telomerase, if cell replicates its genetic material chromosome ends fail to replicate completely. Because, the lagging strand synthesizing DNA polymerase could not fully replicate its 3' ultimate end of the linear DNA molecule. Hence each round of replication cause progressive shortening of chromosome end and that in turn leads loss of functional genes. Cell that lost the functional genes attain senescence (Kuilman et al., 2010; Regulski, 2017).

#### 3.3.2. Inflammation

Currently human beings are living more years than normal, but their age doesn't stop increasing. Ageing is a persistent process that influences all organs, cells, tissues and organisms which decrease homeostasis and increases organism susceptibility (Vasto et al., 2009).

At the extent of cells the human beings are linked with cancer, inflammation and senescence. A genetic process that related with ageing is the production of inflammatory cytokines that represents a crucial mechanism of directs carcinogenesis at cellular level. Change in the production of inflammatory mediator is responsible for ageing; a typical example for senescence is inflammageing. Inflammatory mediators can be regulated to alter the ageing process. Ageing leads to various diseases one among them is cancer. Acute changes in the immune system is the major problem in ageing which results in autoimmune diseases, failure in healing the wounds, no proper response to vaccines, various infectious diseases and cancer. The ageing process affects both innate and adaptive immune system and leads to alterations in the immune cells, lymphoid organs, and circulating soluble factors that affect the microenvironment of the immune cells. A little increase in inflammation is the key factor in ageing which leads to increased vulnerability to inflammatory diseases. “Immunosenescence”, is a term that refers to the slight decline in the immune system which is caused due to the natural ageing process (Bottazzia et al., 2018).

Inflammageing can be due to concomitant increase in proinflammatory status, cell-autonomous alterations and reduction in coping up with various stressors. The various other causes for the inflammageing are failure of the immune system to clear the pathogens and the impaired host cells also called “immunosenescence”, accumulation of proinflammatory tissue damage, senescent cells increases the production of proinflammatory cytokines, increased activation of NF-kB signaling pathway by stress, and decrease in the capacity if autophagy that decreases cellular housekeeping. These changes stimulate production of inflammasomes a danger-sensing multi-protein platform that leads to activation of inflammatory pathways which contributes to various age related disorders including cancer. Chronic inflammation mainly contributes to the cancer that supplies biologically active molecules to the tumor microenvironment like survival factors that reduces cell death, growth factors that triggers cell proliferation, extracellular matrix-modifying enzymes which leads to metastasis, angiogenesis and invasion and proangiogenic factors (Shivapriya et al., 2022).

The immuodefeciency due to ageing leads to cancer incidence is the major problem for the mankind. In comparison with the younger population the older population is found to have little less frequency of naïve CD4þ T cells and very low frequency of naive CD8þ T cells in the peripheral blood, this is mainly due to the naïve cells to memory cells due to the exposure to immune challenges. The age related decrease in the circulating immune cells which is the main consequences for carcinogenesis is found to be undetermined. On the contrary the difference between

younger and older individual for other immune compartments including dendritic cells, B cells, and NK cells are subtler.

On the other hand the cancer that is associated with immunodeficiencies like patients with organ transplantation, AIDS are mainly virus-induced (e.g., leukemia, Kaposi's sarcoma, and lymphoma), these are not common cancers in elder peoples. Furthermore the immunotherapy to treat cancer in older individuals is less effective because of the reason that ageing reduces the ability of the T cells to recognize and atop tumor progression because of the process called immunosenescence. But an advanced treatment strategy for melanoma is with -CTLA-4 antibodies which is effective in both elder and younger population. To conclude with, even though we have enough data that indicates that the ageing is mainly due to inflammation that also promotes tumor, the mechanism behind functional decline of the immune system in ageing that leads to carcinogenesis is still not clear. The clarity in this aspect will have a great impact in the medicinal field to treat cancer in the older individuals as it is proved recently that the cancer immunotherapy increase the survival rate of patients even ion advanced stage (Song, 2019).

### 3.3.3. Glycation

Non-enzymatic glycation or glycoxidation chemical reaction that produces heterogamous end products containing reducing sugar is called Maillard reaction (Monnier and Cerami et al., 1981). During this reaction reversible Schiff-base adducts formed by the reaction between, free amino group bearing biomolecules such as amino acids, amines, proteins, lipids and nucleotides reacts with aldehyde functional group present in glucose, fructose and hexose-phosphates. Schiff-base adducts eventually converted to Amadori products, Subsequently $Fe^{2+}$ , $Cu^{2+}$ , or hydroxyl radicals oxydize them in to stable products called as Advanced Glycation End Products (AGEs) (Tessier, 2010). In addition to these endogenous AGE's some processed protein rich food and tobacco smoking are also considered as source of exogenous AGE's (Nguyen, 2006).

Over a period of time both endogenous and exogenous AGE's renders irreversible damage to the biological macromolecules, altering their structural and functional integrity. Accumulated AGEs contribute to age related inflammation. They could acts as ligands for cellular receptors and modulate several pro- and anti-inflammatory effects (Chaudhuri et al., 2018). Various cell types including monocytes, macrophages, microglia, astrocytes, neurons, smooth muscle and endothelial cells are reported to contain high-affinity receptor for AGE's called as Receptor for advanced glycation end Products (RAGE). RAGE are multi-ligand receptor belongs to immunoglobulin superfamily known to regulates immune responses and inflammation

(Donato, 2007). Upon AGE's binding RAGE initiates series of cellular signaling cascades such as activation of nuclear factor-kB (NF-kB), oxidative stress, and inflammation. RAGE also stimulates phosphatidylinositol-3 kinase (PI-3K), Ki-Ras and the MAPKs, Erk1, and Erk2, PKC (protein kinase C), Rac/Cdc42, and TIRAP and MyD88 (adaptor proteins for TLR 2 and 4). Activation of all these pathways orchestrates the production of pro-inflammatory cytokines, chemokines, adhesion molecules and oxidative stress and causing inflammation, in turn leads to ageing (Chaudhuri et al., 2018).

The extracellular matrix glycation and ageing: Extracellular matrix is a dynamic 3 dimensional structural scaffold formed by heterogeneous secretory proteins belongs to two main types of glycoproteins: proteoglycans (PGs) and fibrous proteins (Frantz et al., 2010). These PGs and fibrous proteins comprise functional motifs including RGD (arg-gly-asp) and GFOGER (gly-phe-hyp-gly-glu-arg). Arginine residues present in these functional motief is the prime target of glycation reaction, glycation of these residues causes loss of charge and structural distortion (Gautieri et al., 2018). Further, the glycation reactions also mediate the intramolecular cross-linking reactions. Both structural distortions and accumulation of cross linked products lead to decreased binding affinity among the proteins of ECM and leads to cell detachment or thickening of the basement membrane. Finally, the defective interactions between cells and their ECM shift tissues and organ towards the ageing process (Kuzan et al., 2018; Reigle et al., 2008).

### 3.3.4. Mitochondrial distribution, oxygen free radical

Free radicals are usually uncharged short-lived molecule having an unpaired valency electron and typically are unspecific ally highly reactive. Usually oxygen derived free radicals are produced in mitochondria due to incomplete reduction of oxygen molecule. Superoxide radicals, hydroxyl radicals, hydrogen peroxide, peroxyl radicals etc. are highly reactive and may damage the lipids, proteins and nucleic acids thereby hampers the normal physiology. It may lead to metabolic depression and long term such effects lead to early ageing (Gladyshev, 2014). Therefore, free radical generation rate is usually directly proportional to ageing about which detailed mechanism is given in later part of this article.

Gradual rise in global warming is likely to hit the normal physiology of animals and hinder the relationships existing amongst temperature, photoperiod, animal's reproduction and longevity. For example, the life cycle of organisms those who produce gametes in winter season and spawn them in the spring in temperate regions may be affected (Lawrence and Soame, 2004). Ageing and longevity in animals are correlated with each other and the rate of ROS generation may act as a link

between the above two. It is because; fecundity and ability of mitochondria in animals in relation to their colder and warmer habitat have a major role in relation to the current topic. This is because mitochondria act as the epicenter for the production toxic ROS (Paital and Chainy 2012). On the other hand, telomere dysfunction is enhanced the requirement of glucose substitution for the maintenance of energy homeostasis and IGF-1/mTOR-dependent mitochondrial biogenesis in ageing tissues. So, mitochondrial stability and homeostasis seems very important in ROS mediated ageing associated processes (Iftikar et al., 2010). So, mitochondrial distribution per cell in animals with respect to their colder and warmer habitats may be related to their lively activity and longevity.

A precise and appropriate logical argument is made on "Longevity-and-antiageing-secrets.com" [(84)] that vegetation in colder regions lives longer. For example, mosses in tundra climate can live up to 150-200 years and the duration is too shorter when they are transferred to warmer regions. The regions are credited to the high fecundity of their cellular mitochondria coupled with low metabolic rate. So, it is speculated that number of mitochondria is directly proportional to the longevity in animals including human being.

### 3.3.5. Stress

Stress may be defined as any external or internal agents that lead to deviate the normal physiology of cell individually and thereby making eventually dysfunction of organs or whole body. Stress has a direct relation with telomere shortening. Chronic stress accelerates premature ageing by shortening DNA telomeres. A wide range of studies has shown that the stress caused by things like untreated depression, social isolation, long-term unemployment, and anxiety attacks can speed-up the ageing process by shortening the length of each DNA strand (Fougère et al., 2017). So all stress-related changes associated with ageing and factors such as inflammation and sex steroid alterations (may interact with psychosocial stress) can also affect the risk for mood and cognitive disturbance in older individuals. It clearly indicates the tight relation between stress and ageing. Therefore, research on ageing and interventions targeting resilience to stress is highly recommended (Guzik and Touyz, 2017).

### 3.3.6. Disease susceptibility

The dynamic molecular machinery required for maintenance of the structural architecture of cells is mainly made by proteins. At least 30,000 different human proteins are recognized (Herczenik et al., 2008). So, they are important and their synthesis in incorrect shape (misfolded) in cells due to many factors may lead to ageing associated phenomenon. Protein mis-folding animals to increase have a strong

association with temperature, high or low pH, agitation, elevated glucose, or oxidative damages. Under above conditions, an increase in mis-folding rate or denaturation of streptokinase (Azuaga et al., 2002) and β –lactoglobulin (Iametti et al., 1996) at increased temperature and superoxide dismutase (Rakhit et al., 2005), LDL, ApoC-II (Stewart et al., 2007) due to oxidative damages are reported in human. The rate of mis-folding is accelerated by the altered amino acid composition in proteins and leads to mutation. Protein mis-folding and the subsequent aggregation are associated with ageing, often highly debilitating, diseases for which no sufficient cure is available yet Diseases that are associated with protein mis-folding represent a group of disorders that have protein aggregation and plaque formation in common (Trotter et al., 2001).

Amyloidosis is a group of diseases that deals with such mis-folded proteins. Under such cases, protein aggregates accumulate either systemically or locally in certain organs or tissues. Many neurodegenerative diseases namely Alzheimer's disease (Amyloid- β, tau), Parkinson's disease (α-synuclein), Huntington's disease (Huntington), familial British dementia (Abri), Spongiform encephalopathies (Prion), hereditary cerebral hemorrhage with amyloidosis (cystatin C), amyotrophic lateral sclerosis (CuZn superoxide dismutase) and other diseases such as diabetes mellitus (IAPP, amylin), atherosclerosis (modified lactate dehydrogenase) and sickle cell anemia (hemoglobin) are found to be the leading protein disorder related diseases and lead to early ageing (Herczenik and Gebbink, 2008). These protein mis-folding diseases share similar pathological aspects including hypertension, OS, or hyperglycemia. Interestingly, all of these can result in ageing too (Chaudhuri and Paul, 2006). So, OS in one hand and increases the risk of protein mis-folding and disease susceptibility on the other hand in animals including humans may influence the longevity in animals.

### 3.4. Effects of nano-particle, a new horizon

Nanoparticles (NPs) are materials of the diameter that fit within a few hundred nanometers. This size provides them with bodily and chemical residences in order to make them highly bioavailable (ISO /TR 27628, 2007, Ostiguy et al., 2006, Handy et al., 2008). NPs find huge potential in medical applications and produced by means of chemical processes which are further used in different fields like fertilizers, biomedicine, electrical appliances, pharmacology and cosmetics (Matranga and Corsi, 2012). Research done on this revealed that Ag-NPs, $TiO_2$-NPs, and ZnO-NPs turn to be toxic for marine species (Gottschalk et al., 2009). NPs are discovered in water and land ecosystems, where they are consumed by biotic creatures wherein they acquire, before removal by means of the defense machine or other metabolic pathways. In organisms, NPs comprise molecules with unique chemistry; intrude with the ordinary physiological machineries of the foetus, young animals, and grown-ups. These

mechanisms involve in their ageing and senescence of cells through tissue remodelling and mesenchymal transition (Exbrayat et al., 2015).

### 3.4.1. The mechanism of ageing under nano-particle exposure

Ageing affects almost all the tissues on continuous exposure to nanoparticles as they are busy generating ROS mediated tissue destruction. They are classified into chronological and photo-ageing which affects the dermal and epidermal tissue layers largely. The cellular and metabolic abnormalities could be noted in these cells such as production of excessive elastin, thickening of collagen fibres and keratinocyte irregularity. They could be monitored clinically through external physiological changes also (Mukherjee et al., 2006). Oxidative damage is prompted by internal or external reactive oxygen species (ROS) that can motive harm to a chain of cellular additives, for biomolecules like DNA/RNA, cellular proteins, phospholipids and so on. Mitochondrial breathing converts oxygen into a series of reactive components, mainly $O_2$ and (OH) loose radicals, and results in oxidative related random deletions that harm and spread to tissues (Muller et al., 2007, Wenshu et al., 2015).

### 3.4.2. Effects of NPs on Terrestrial Animals Species

Today, numerous residing models are used a good way to understand the influences of NPs on animals. Research involving mammals, which include mice, or small fishes, along with the zebra fish, proved that nanoparticles produced deadly results at the developmental stages of embryos (Blum et al., 2012, Sun et al., 2013). Some experiments involving in vitro and in vivo cultures of animal tissues exhibited that silver nanomaterials brought about an oxidative pressure featured by properly reactive moieties possessing unfastened oxygen radicals (ROS), geno toxicity with DNA smash, or apoptosis leading to senescence and death (Kim et al., 2013). Studies concerning the ecological impact of fabricated nanoparticles are hindered by way of the lack of queries to locate and estimate them in water, land, and animals. Neutron activated experiments has been extensively performed to look at the results of Cobalt nanomaterials in the earthworm *Eisenia fetida* (Oughton et al., 2008). Few experiments completed with mice showed actual lethal consequences of NPs on cognitive and behavioral disorders. In the rats, short exposures to Cu-NPs (forty and 60 nm diameter) triggered the multiplication of endothelium of brain vessels once they had been introduced to lower concentrations (approximately 1.5 $\mu$g/mL). Higher concentrations (50 $\mu$g/mL) brought on a boom of prostaglandin (Trickler et al., 2012).

Ag-NPs kindled the thinning effect of the body in rats, with a decrease in its propulsive pastime. The damage of glial cells and reduction of myelin fibre in tissues tend to activate heat shock proteins due to the accumulation of ultrafine nanoparticles in blood brain fluxes promoting neuronal accidents (Trickler et al., 2010). Another

study conducted on rat models revealed a short term treatment to Ag-NPs stimulated the blood-brain barrier, promoting a pro inflammatory response that may broaden a brain infection followed with neurotoxic results. Cytotoxic outcomes were induced via the smallest NPs in comparison to largest ones (Exbrayat et al., 2015).

### 3.4.3. Influence of metallic nanoparticles in ageing

Metallic nanoparticles are widely being used in food industries, medicine and pharmaceutics. Silver nanoparticles are largely active and can penetrate blood brain barrier which accumulates there in high amounts. These particles are involved in influencing the cognitive and behavioral properties of animals. Ex vivo experiments have demonstrated the appearance of ROS in cells and found to influence calcium signals in experimentations (Antsiferova et al., 2018, Kim et al., 2014). Nanoparticles including silver and oxides of zinc and copper are regularly used as microbicidal agents. Still, after the release of pollutants into the ecosystem, harmful results also can have an effect on non-target organisms (Sharma et al., 2009). The effects of copper and silver nanoparticlesin the size range of 50 to 60 nm have been more essential than aluminum nanoparticles with sizes of 50 to 60 nm. It became additionally found that the consequences have been more crucial in rats than those of mice (Zhiquan et al., 2018).

### 3.4.4. Influence of nano-plastics in ageing

Occurrence of nanoplastics in water bodies is a prevalent concern besides their toxicity and other hazardous effects. Prolonged exposure to polystyrene like nanoplastics are posing age related problems and paves a dangerous way for their senescence and cell death, as per the studies done in small animals. One of the major model species is water flea, Daphnia pulex which has expressed stress genes and provoked physiological changes. These changes recorded could be attributed to all other aquatic animals exposed to such nanoplastics. Polystyrene nanoplastics and their dispersants have reported to stimulate the production of ROS and developmental defects in the larvae of sea urchins. They can cross blood brain barriers and hence affect the metabolism and behavior of fishes like *Carassius carassius* which are further associated with the senescence and ageing of cells (Koelmans et al., 2015, Spannbrucker, 2019).

### 3.5.5. Influence of carbon nanoparticles in ageing

Senescence of lung epithelial cells has been observed on inhalation of combustion derived carbon nanoparticles (Bartling and Hofmann 2018). Diseases related to ageing and senescence such as the chronic pulmonary disease and pulmonary fibrosis also has been reported. Repetitive exposure to carbon nanoparticles have shown to produce senescent like phenotype which results in the loss of function of

communication in gap junctions. Prolonged doses of carbon nanoparticles stimulated ageing in cells and provoked age related diseases (Wenshu et al., 2015).

### 3.4.6. Application studies of Fullerene in ageing of animals

Fullerenes and their derivatives have fascinated sizeable interest in biomedicine. Polyhydroxyl fullerene (fullerenol), a soluble fullerene derivative, is confirmed as an appealing antioxidant. To similarly determine their anti-aging and anti-stress ability, *Caenorhabditis elegans* (*C. elegans*) has been utilized as a small animal model to assess the impact of fullerenol on the growth, conduct and anti-stress ability features in vivo. The records display that fullerenol has very little manifestly toxicity on nematodes and can postpone *C. elegans* ageing underneath regular circumstance. Further research displays that fullerenols attenuate endogenous ranges of ROS generation and presents defense to C. elegans under pressurized conditions by up-regulation of genes for stress regulation and improves lifespan (Jun et al., 2010). Functionalized fullerenes stimulate key organic responses, along with cell viability, intracellular ROS, cellular proliferation and cellular cycle reactions. These molecular mechanisms have been attributed to the variations in expressing the HERC5 genes of the Ubiquitin family (Svetlana et al., 2020).

### 3.4.7. Nano-ageing, an emerging science

Impact of nanoparticles on cellular and physiological senescence is largely an unexplored research area (Chen-Chen and Xiaoxiao, 2021). To date, few works concerning the outcomes of NPs on species residing in soil like small mammals or worms, semi aquatic animals, which include amphibians, freshwater or marine species, together with Pisces, invertebrates, phyto and zooplankton have been performed. Research on the influence of nanoparticles on aging is divided into 2 predominant streams: one being the exploration of numerous pathophysiological and molecular activities accountable for growing older and the other being research on various anti-growing old dealers. Although an awful lot tricky mechanistic studies were performed for know-how the pathophysiology of growing older, they will nevertheless preserve until the entire cascade of molecular activities answerable for intrinsic/photo aging is elucidated. Under normal lifestyle conditions, nanoparticles induce a delayed ageing in worms. Meanwhile, underneath oxidative pressure, nanoparticles show obvious anti-stress impact with the help of its ROS engulfing property at cellular levels and by the up regulation of numerous stress reducing genes (Hui et al., 2022). Nanoparticles are found to behave indifferently both up-regulating and down-regulating the ageing phenomena based on their particle size, surface characteristics and dosage.

### 3.5. Hormonal regulation and endocrine disruption

Hormones are important molecules that render heavy duty on maintaining the normal physiology in animals (Sahoo et al., 2023). Their titre is highly crucial in ageing individuals. It is because they have an intricate relation with the metabolism and many clinical consequences. On one hand, titre of two major sex hormone i.e. oestrogen and testosterone declines at the peripheral level with age and on the other hand it is coupled with an increase in luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin. Also an aged person experiences alleviation in the level of growth hormone, insulin-like growth factor-I and dehydroepiandrosterone and its sulphate-bound form in serum. Although, structurally, major changes are found in hypothalmo-pituitary-adrenal/thyroid axis, functionally less change is noticed in adrenal and thyroid hormones as a function of ageing. Altogether, these hormonal changes lead to compromised protein synthesis, reduction in lean body and bone mass, augmented fat in body, insulin resistance, higher cardiovascular disease risk, increase in vasomotor symptoms, fatigue, depression, anaemia, poor libido, hampered erectile functions, and finally the reduced immunity (Chahal and Drake, 2007). Therefore, hormonal therapy many a time is referred in elders. It is very clear that hormonal deregulation at ageing is a fundamental rule to be followed in body. It creates several health challenges. The hormonal deregulation is associated with many clinical consequences such as an increased risk of atrial fibrillation and metabolic depression. Therefore, hormonal longevity pathways offers key to new drugs to fight with ageing (Jones and Boelaert, 2015).

The mechanism of change in hormonal deregulation with ageing is attributed to both structural and functional aspects of the endocrine glands. Degeneration of the gland structures and low secretory pattern of the sensitivity hormones are regulated by negative feedback by end hormones. Chronic diseases, inflammation, low nutritional status etc in elders increases with hormonal deregulation. Overall it decreases bodily functions, thereby, increases ageing. Therefore, hormonal homoeostasis and ageing are interconnected and hormonal therapy may decline ageing process or reverse early ageing (van den Beld et al., 2018).

## Conclusion

The causes of aging are diverse and intricately connected, involving a combination of genetic, molecular, and environmental factors. Scientific research has identified several fundamental processes—such as DNA damage, telomere shortening, epigenetic changes, oxidative stress, and mitochondrial dysfunction—that collectively contribute to the progressive decline in biological function. These mechanisms, often referred to as the hallmarks of aging, not only explain why organisms age but also offer potential targets for slowing or modifying the aging process. In particular, the role of

microRNAs and epigenetic regulation has emerged as a significant factor in controlling gene expression patterns that change with age. While aging is a natural and inevitable process, understanding its underlying causes enables us to explore strategies to delay its effects, prevent age-related diseases, and promote a longer, healthier life. Continued research in the biology of aging holds great promise for improving human health span alongside lifespan.

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