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Review Article

Telomere Shortening as Biological Hallmark of Cellular Senescence and Longevity-An Update

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ABSTRACT

The process of ageing is the consequence of both genetic and epigenetic alterations associated with metabolic disorders and characterized by mitochondrial dysfunctions generated due to reactive oxygen species. Current reports indicate that cellular ageing or senescence retrograde mitochondrial signaling disorders, telomere shortening, heterochromatin configuration, endoplasmic reticulum strain and unfolded protein responses. Supplemental vitamins, inhibition of cell cycle arrest and controlled expressions of tumor promoting genes *p53*, $p21^{CIP1}$ and $p16^{INK4a}$ are robust telomere length longevity promoting interventions and prolong youthful cell functions. This review is aimed to provide an update on the molecular approach mediating the cellular ageing in developmental and programmed replicative ageing cascade with focus on DNA damage response in various cell types. Through rational ideas and critical investigation, we conclude that the combination of irretrievable alternations caused by metabolic reactions elicit the accelerated mechanisms of cellular ageing.

Keywords: DNA Damage Response (DDR), Mitochondrial signaling, Tumorigenesis, Telomerase

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INTRODUCTION

The process of ageing or senescence is a degenerative process derived from a variety of distinct complex mechanisms which is implicated by different physiological, biochemical and molecular factors. The pathophysiology of aging is directly related to oxidative stress caused due to the overproduction of reactive oxygen species, thereby deteriorating DNA and is responsible for cellular transformation, carcinogenesis, mutations, vascular endothelial dysfunctions, atherosclerosis, neuro-oxidative stresses such as Parkinson's disease, Alzheimer's dementia and various age related syndromes. Until now different theories have defined the ageing process, each from different point of view (Adam R, *et al*., 2017). The most recent and strongest study supports the statistical progressive idea that oxidative stress is a substantial biomarker of ageing and probability of death increases with the age of the organism at any time.

The first proposed theory by Harman in 1950s was known as 'free radical theory of ageing' which was based on the fact of mitochondrial production of reactive oxygen species. It was stated as the age of the organisms can be determined by the degree of accumulation of free radical deterioration with the passage of time and increase in ROS generation accompany aging resulting in oxidative damage, functional alterations, pathological complications and eventually death. The biochemical and molecular mechanism of aging is associated with mitochondrial damage because it is the major site of ROS production and intracellular oxygen consumption from the electron transport chain and nitric oxide synthase reactions. Hydrogen peroxide and complex reactive oxygen species produced in human mitochondrial matrix are chemical signal molecules which regulate the whole cellular growth, aging and proliferation processes (Shekhidem AH, *et al*., 2019). The most commonly produced reactive oxygen species are superoxide and nitric oxide radicals in the presence of NADPH oxidases and nitric oxide synthase which highly regulate the whole metabolism of the human body including calcium ion concentration, activation of proteins such as glutathione (GSH) and modulation of signal transduction proteins such as protein kinase C, tyrosine kinase and Ca^{+2}-ATPase responsible for aging and cell growth.

This redox regulation also causes many disorders associated with aging process (*Figure 1*). Ageing tissues experience a progressive decline in homeostatic and regenerative capacities which has been attributed to degenerative changes in the aged cells. This proposed mechanism involved in age dependent deterioration of cells is important to develop new therapies to slow down the ageing process and to wipe out the age related diseases that target the specific causes of age related functional decline.

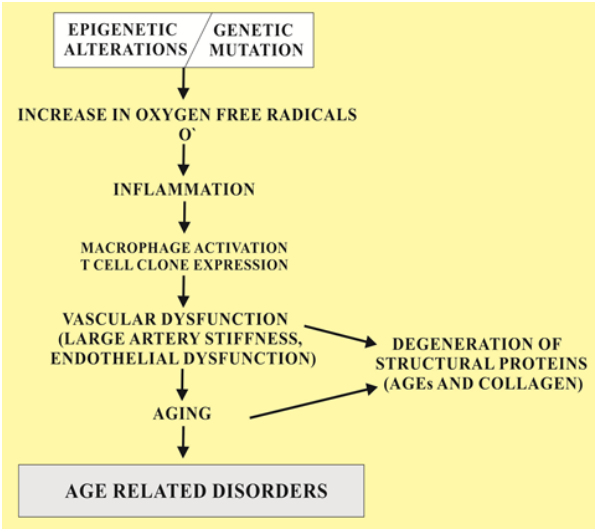

Figure 1: Proposed mechanism of ageing

The industrious exploration of geneticists has led to the discovery of many age-related genes which code for various transcriptional longevity proteins. These are categorized into four groups i.e. anti-stress genes (for example: Antioxidative stress proteins), metabolic regulator genes (for example: Insulin/IGF-1 signaling proteins, mitochondrial enzymes and cholesterol synthesis genes), mutation repairing genes (nuclear stability genes) and homeostasis proteins (hormone synthesis in a regular pattern). Some of the age-related genes been discovered are hsp-16, hsp-70, KLOTHO, *HSF-1*, isp-1, ras2p, lac-1, *lag-1, PCMT, daf-2, DAF-16*, daf-23,

AGE-1, CLK-1, Pit-1, *SOD-1, mth*, α-MUPA, p66sh, *PROP-1, SAG, spe-26, SIRT1* etc. (Aksenova AY and Mirkin SM, 2019). Other cellular proliferators such as IGF-1, MAPK, *PI3K*, P16 and *CDK1* also regulate the cellular longevity. With respect to the physiology and pathology of a biological system, aging is related to the genetic networks that work in a synchronized manner to resist various environmental injuries. Thus, aging is a complex interaction of both intrinsic and acquired factors which focus on damage restoration and capability of defensive renovation (AFfAR AF, 2016).

LITERATURE REVIEW

Molecular mechanism of cellular aging

Multiple studies demonstrate that ageing of differentiated cells significantly demonstrates the age related damage to distinct cellular organelles and their associated functions. For example, mitochondrial DNA (mtDNA) mutations which are maternally transmitted underpin brain ageing related disorders. Similarly, endoplasmic reticulum and protein misfolding stress also participated in ageing of brain lesions and increased production of mitochondrial DNA denotes cardiac ageing process. A research study conducted on muscle cell ageing demonstrated that eukaryotic initiation factor 4E-Binding Protein (4E-BP) which is transcribed by the Fork Head Box O (*FOXO*) transcription factor through the autophagy lysosome system alleviates the muscle cell ageing due to the aggregation of protein. Specific oxidative agents which create oxidative stress in cellular organelles such as endoplasmic reticulum, mitochondria and lysosomes that accelerate the process of cellular ageing resulting in the loss of intrinsic cellular function (Arai Y, *et al*., 2015). The ageing spectrum of differentiated cells is broad as compared to the non-dividing cells because the cumulative damage to differentiated cells causes genetic and epigenetic alterations showing greater DNA Damage Response (DDR) in proliferating cells known as mitotic stress. However, the cell ageing is basically triggered by DNA damage response. The ageing of cell is identified by two types of factors i.e. replicative ageing and Oncogene (stress) Induced Premature Senescence (OIS). Multiple lines of evidence indicate that shortening of telomeres act as a biological clock which causes hematopoietic stem cells and cancerous cells to show replicative ageing.

During the process of telomere shortening, the DNA Damage Response (DDR) kinases recruit Ataxia Telangiectasia Mutated (ATM), ataxia telangiectasia and Rad3 ATR to the altered foci of single and double stranded DNA resulting in DNA damage and activate *p53* and $p21^{CIP1}$. These activated genes trigger the cell cycle break due to which OIS separates the dividing the cells from the proliferative pool of cells. Thus, this crafted OIS creates a specific pathophysiological barrier to knock out tumor formation (Carvalho AC, *et al*., 2019) (*Figure 2*). Damage to mtDNA and organelles by free radicals leads to loss of mitochondrial function and loss of cellular energy. Mutations in mtDNA occur at 10-20 times the rate seen in nuclear DNA. A significant portion of ageing may be due to mtDNA deletions from singlet oxygen induced by ultraviolet light. Ageing mitochondria become enlarged. Ageing leads to the decline in coenzyme Q which is an important part of antioxadative defence system. In contrast to the normal human cells which undergo ageing (cell senescence) by the inhibition of DDR related OIS and activation of H-Ras V12 oncogene. The oncogene induced DNA replication activate both DDR and OIS which craft alternative changes in the succession of DNA replication fork with active replicons. When the progression of DNA replication fork and DNA double strand break is prematurely suppressed, it activates OIS resulting in accelerated carcinogenesis in albino mice. During the process of ageing, the senescent cells undergo increased activity of senescent associated β-galatosidase (SA-βGAl), Senescence Associated Heterochromatin Foci (SAHF) which ultimately aggravate histone H3 lysine 9 trimethylation (H3K9me3) and heterochromatin protein 1 ϒ (HP1ϒ) activity. It is very important in cellular senescence to amplify the levels of cyclin dependent protein kinase inhibitors $p16^{INK4a}$ and $p21^{CIP1}$ in order to break cell cycle crafting a crucial halt in tumor formation (Arbeev KG, *et al*., 2020).

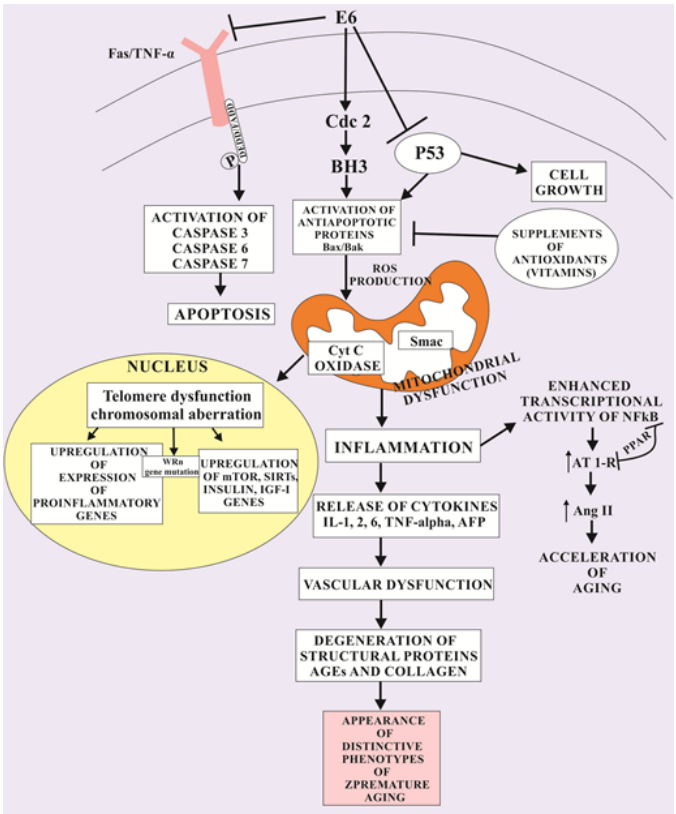

Figure 2: Schematic diagram of molecular and biochemical mechanism of cell senescence

Molecular biology of Developmental and Programmed Senescence (DPS)

The physiology of cellular ageing in developing embryonic tissues of nude mice is based on the recruitment of SA-βFal, H3K9me3, $p21^{CIP1}$ and (HP1ϒ) activation and deactivation of cell proliferation biomarker *Ki67* and Bromodeoxyuridine (BrdU) in embryonic tissues. The molecular mechanistic approach determined that there is specific difference between Development and Programmed Senescence (DPS) and OIS and replicative senescence such that DPS system is devoid of DDR-ATM-*p53* genes and p38 and $p16^{INK4a}$ oncogenes instead is related to the cascade signalling Smad and $p21^{CIP1}$. One of the most important feature of DPS is that it is associated with inflammatory cytokines and transforming growth factor β. However, many characteristics of DPS and OIS are common in them such as Upregulated gene expression of $p15^{INK4b}$, SASP mediators, mitogen activated protein kinases and nuclear factor kappa-B signaling (Astuti Y, *et al*., 2017). SASP is indicated to control paracrine senescence mediating Vascular Endothelial Growth Factor (VEGF) and Tumor Growth Factor (TGF-β) which in turn regulates the genetic expression of $p15^{INK4b}$ and $p21^{CIP1}$.

The mechanism of induction of DPS and its regulation by TGF-β is quite interesting. The cytokine family of TGF-β plays a crucial role in the maintenance of telomeres during the development of tumor. It helps in tissue remodeling, the hurdles of transplantations and inflammatory processes. However, Smad3 represses the Telomerase Reverse Transcriptase (*TERT*) gene being regulated by a number of cytokines. Instead, the checkpoints of telomere DNA double strand being $p16^{INK4a}$ and $p15^{INK4b}$ shows a putative mechanism of activation and cytokine induced telomerase inhibition. The eventual destiny of aged cells is apoptosis and clearance medi-

ated by macrophages. Multiple researches indicate that developmental and programmed ageing is seen only in tissues with developmental birth abnormalities. A recent study also disclosed molecular biomarkers of cellular ageing in human placental syncytiotrophoblast during embryonic development. During the formation of embryo, the Human Endogenous Retrovirus-W-1 (ERVWE1) is involved in the formation of syncytiotrophoblast which acts as an interface between maternal and fetal tissues at the placenta mediating cellular fusion. However, in case of cellular senescence (ageing), the genetic expression of ERVWE1 causes hyperploid syncytia through the mechanism of *p53* and p16-pRb signalling cascades exhibiting the process of aging (Aubert G, *et al*., 2012).

Mediation of cellular ageing by telomerase and telomere repeating units of RNA

Telomeres are the repeating DNA sequences of TTAGGG associated with the binding molecules at the end of each linear chromosome in all nucleated cells which do not fully replicate by DNA polymerases. Telomeres show variation in length from 4 to 14 kb which is maintained by a ribonucleic enzyme "telomerase" which add telomere repeating sequences to the ends of chromosomes. Thus, telomere shortening could be a biological prognostic biomarker that signals the replicative ageing, disease and premature morbidity in all cultured primary human cells. During the phase of mitosis, the cell chromosome undergoes replication (duplication) maintaining the length of telomeres.

Thus, every unit increase in the length of telomere reflects the number of replications happening in mitosis. Upon the achievement of specific length, the shortest telomere activates DNA Damage Response (DDR) element for cellular ageing (Aubert G, *et al*., 2012). In spite of this fact, many critical diseases such as heart diseases, immune-compromising and psychological disorders involve telomere shortening often diagnosed in peripheral blood leukocyte count. Thus, the degree of shortening of telomeres determines the degree of stress in the body. For example, in healthy women with premenopausal condition, increased mitochondrial oxidative stress is associated with telomere length determined in peripheral blood leukocytes. The women which depicted increased level of oxidative stress had shorter telomeres compared with females having lower levels of oxidative stress. Evidence indicated that sedentary lifestyles cause this telomere shortening and improved diet, stress management and comprehensive living improve the telomere length both qualitatively and quantitatively (Aunan JR, *et al*., 2016).

DISCUSSION

Current research reported that a non-coding telomere unit of RNA (TERRA) code for telomere shortening causing the aggregation of TERRA molecules in nuclear centre. The human repeating units of UUAGGG of TERRA sequences form guanine quadruplexes (G- quadruplexes) leading to the formation of RNA: DNA hybrid loop. The RNase H enzyme in eukaryotes removes the RNA moiety from the telomeres containing RNA TERRA. Telomere shortening can also be induced by exonuclease-1 which resects the ends of chromosomes producing replication stress mediated telomere short phenotype. An important feature of TERRA is that it removes the heterogeneous nuclear ribonucleoprotein A1 (*HNRNPA1*) thus, prevents the binding of telomere 1 (POT1) to telomere of the single stranded DNA (ssDNA) leading to the telomeric stress. In spite of the TERRA regulation in telomere shortening, TERRA forms aggregates in extremely proliferating cancerous cells which indicate large diameter nuclear centers different from the phosphorylated histone H2AXY nuclear foci and normal progenitor neuronal cells of under developing cerebellum. This fact suggested that elevated TERRA in the chromosomes might act as prognostic biomarker of early telomere shortening during the early development of tumor and replication stress (Aviv A and Levy D, 2019). Various factors which alter the length of the telomere and consequently the activity of the telomerase are depicted in Table 1.

Table 1: List of biochemical and physiological factors that alter the length of the telomere

Factors	Description	References
Oxidative stress	Oxidative stress is an important aspect of toxicology associated with telomere shortening	(Aviv A and Shay JW, 2018)
Immune response	High level of T-lymphocytes (CD8 and $CD28^+$) in elder patients is associated with blunted immune risk. Telomerase induction is a solution to this immune response	(Banszerus VL, *et al*., 2019)
Chronic inflammation	Short telomere is associated with inflammatory disease e.g. rheumatoid arthritis	(Barnes RP, *et al*., 2019)
Insulin resistance	Inhibition of Insulin like growth factor-I signaling is a prompt cell longevity promoter	(Barnett AG, *et al*., 2005)
Menopause	There is a strong dependency of hormones on telomere length with milestones of aging	(Beijers R, *et al*., 2020)
Telomerase	Length of the telomere is shortened due the down regulation of telomerase expression	(Bell CG, *et al*., 2019)
Genetic transfer	The trait of telomere shortening is transferred from parents to the offspring (For example: Dolly sheep)	(Belsky DW, *et al*., 2018)
Metabolic syndromes	Type 2 diabetes and metabolic syndrome X are metabolic syndromes of premature aging	(Belsky J and Shalev I, 2016)
Gender	Telomere length tend to be longer in females than in males	(Benetos A, *et al*., 2013)
Age	Younger age individuals (children and adults) have longer telomeres as compared to the older individuals	(de Jesus BB and Blasco MA, 2011)

Cell cycle arrest induced by cellular ageing

B-Raf is known to induce cell cycle arrest by a complex mechanism of inhibition of pyruvate dehydrogenase kinase 1 (*PDK-1*) and over expression of pyruvate dehydrogenase phosphatase 2 (*PDP 2*). As a result, the pyruvate is increased due to the elevated levels of Pyruvate Dehydrogenase (PDH) in citric acid cycle (Krebs' cycle). The resultant electron transport chain is up regulated crafting redox stress which ultimately leads to the cellular ageing. The normal levels of pyruvate dehydrogenase phosphatase 2 and pyruvate dehydrogenase kinase 1 cause the downregulation of PDH and elevated OIS which ultimately leads to the synthesis of melanoma. Another important fact supported by many evidences is that the stimulation of PDH also causes the activation of *p53* and $p21^{CIP1}$ induced DNA damage response (*Figure 3*). Cancer and ageing are both accompanied by cellular damage. Cancer and cell longevity require a durable cell proliferation potential. Therefore, this mechanism limit the indefinite proliferation provide cancer protection that favor ageing. The overall balance between these convergent and divergent mechanisms ensures cancer free and healthy life until late adulthood for most individuals. The malate enzymes i.e. ME-1 and ME-2 also increases the expression of OIS in albino mice models. The specific reason of down regulated expression of malate enzymes ME-1 and ME-2 in OIS is supported by the relationship of tumor suppressor gene *p53*. However, it is a clear fact that *p53* is inhibited by ME-1 and ME-2

in normal circumstances through the activation of AMP-activated protein kinase-A consequencing in the acceleration of ageing process. The convergence of the metabolic pathways of PDH, *PDP2*, ME-1 and ME-2 can elucidate the interconnection of replicative ageing and OIS (Bettin N, *et al*., 2019).

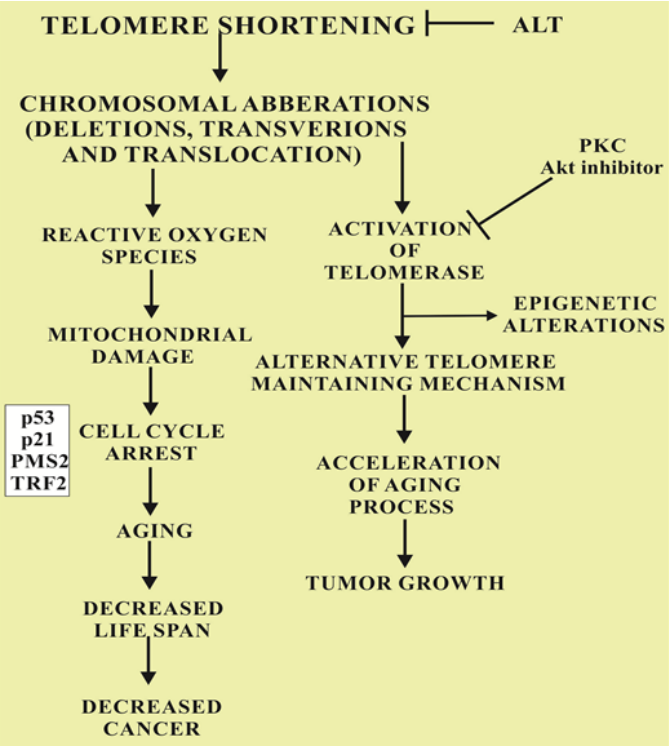

Figure 3: Model of telomere shortening during cellular senescence

Various antioxidants and nutraceutical which are responsible for active targeting of the telomere activity are depicted in Tables 2 and 3.

Table 2: Modulation of telomere structure and function by nutraceuticals

Nutraceuticals	Modulation	References
Omega 3 fatty acids	Recent study of coronary heart disease patients reveal that there is an inverse relationship between levels of omega 3 fatty acids in blood and telomere shortening over a period of five years	(Boccardi M and Boccardi V, 2019)
Vitamin D	Vitamin D is an inducer of telomere length	(Bodelon C, *et al*., 2014)
Nicotinamide	Nicotinamide increases the life span of the fibroblasts in human beings due to the reduced production of ROS in mitochondria	(Calado RT and Dumitriu B, 2013)
Multivitamins	Use of multivitamins increases the telomere length, hence, improving the life span	(Canudas S, *et al*., 2020)
Folate B12	Folate increases the length of the telomere in a non-linear manner by changing the DNA integrity and epigenetic alterations. However, decreased telomere length is associated with older males	(Celtikci B, *et al*., 2021)
Statins	Statins control the ROS balance of endothelial cells and increases the telomere length of lymphocytes	(Chen BH, *et al*., 2017)
Gingko biloba	Standardized extracts of *Gingko biloba* delay the onset of ageing by upregulating the signaling of P13kinase/Akt that increases the telomerase activity	(Chen R, *et al*., 2020)
Alpha-tocopherol	Also called vitamin E which is indicated to increase the telomerase activity of microvascular cells of the brain	(Chen W, *et al*., 2011)
N-acetylcystein	N-acetylcystein delays the onset of ageing by a complex mechanism of hTERT by blocking its entrance into the cell cytosol	(Cheng G, *et al*., 2013)
Antioxidants	Low levels of antioxidants is reported to increase the rate of breast cancer in females and prostate cancer in males	(Dagnall CL, *et al*., 2017)

Table 3: Antioxidative therapy of ageing

Antioxidants	Proposed mechanism of slowing down of ageing	Interventions in preclinical trials	References
Vitamin E Idebenone clioquinol	The mitochondrial dysfunctioning disrupts cytochrome c oxidase activity, ultimately disturbs various homeostasis mechanisms	Caloric restricted diet administered in albino mice at 1 mg/kg body weight	(de Pedro N, *et al*., 2020)
Vitamin C and E	Neuronal dysfunction is generated in dopaminergic neurons producing endogenous and exogenous toxic secondary metabolites	Reduction of coenzyme Q and creatinine	(Delgado DA, *et al*., 2019)
Beta carotene	Several mitochondrial mutations occur due to SOD1 mutations resulting in loss of mitochondrial membrane potential	Creatinine and coenzyme Q	(Demanelis K, *et al*., 2020)
Deferoxamine	Iron metabolism is deteriorated due to the loss of iron sulfur enzymes	Histone deacetylase inhibitors CoQ	(Der G, *et al*., 2012)
Clioquinol	Impaired iron metabolism due to mtDNA mutations	Idebenone (Histone aceylase inhibitor)	(Dhabhar FS, *et al*., 2012)
Flavonoids	Reactive oxygen species generated in SOD1 mutations	Reduction in mitochondrial enzymes	(Dixit S, *et al*., 2019)
Selenium	Mitochondrial dysfunctions due to genetic mutations	Histone modification	(Dlouha D, *et al*., 2014)

***Mediation of cellular senescence through* p53, p21^{CIP1} *and* P16^{INK4a}**

Peroxisome proliferator-activated receptor (PPAR)-β/δ causes the inhibition of skin tumerogenesis by activating *p53* dependent OIS. The increased expression of peroxisome proliferator-activated receptor (PPAR)-β/δ causes the phosphorylation of ERK thereby increasing the activity of kinase and down regulating p-AKT expression. This decreased p-AKT activity leads

to the progression of cellular senescence by up regulating the expression of *p53* and p27 (Daniali L, *et al*., 2013). The *p53* protein 2 (ASPP2/53BP2L) is activated by tumor suppressor apoptosis gene which indirectly enhances the expression of *p53* dependent apoptosis protein containing active C-terminal *p53* binding domain. This *p53* protein 2 has strong association with *RAS* by binding to its N-terminal domain resulting in the binding of Ras-GTP ultimately activating the *RAS* induced molecular senescence in non-transformed human cells (Eisenberg DT and Kuzawa CW, 2018).

Another inhibitor protein of cell senescence, Yes-Associated Protein (YAP) plays a crucial role in slowing down the cellular ageing process (Eisenberg DT, 2014). The deficiency of YAP activated cellular replicative ageing mechanism through the mediation of *p53*-p16-Rb protein and TEAD-Cdk6 dependent mechanisms. A recent study reported that the promoting of activity of SAHF protein causes the dissociation of oncogene induced tumor suppressor gene *BRCA1* from the cellular chromatin which leads to its down regulation which drives the process of ageing further (El-Chemaly S, *et al*., 2018). The chromatin-remodeling factor associates with *BRCA1* and carries out the phosphorylation of Retinoblastoma Protein (pRb) which activates the Brahma-related gene 1 (*BRG1*) causing the formation of SAHF protein and cellular senescence is induced by the degradation of oncogenic protein Ras and *BRCA1* (Entringer S, *et al*., 2018). The up regulation of SAHF causes the induction of *BRG1* and cellular ageing processes induced by chromatin dependent mechanisms. However, the stimulation of SAHF and *BRG1* is inhibited by reducing pRb, $p21^{CIPI}$ and $p16^{INK4a}$. Therefore, *BRG1* is reported to down regulate *BRCA1* and up regulate *RAS* activity and pRb, $p21^{CIPI}$ and $p16^{INK4a}$ to increase the process of cellular ageing or senescence (de Meyer T, *et al*., 2018).

CONCLUSION AND FUTURE PROSPECTS

The activity of telomerase is a very important step towards the maintenance of life span of an organism. Telomere length as well as the production of telomerase plays the crucial role as the cellular targets of the viability and longevity of the cells. We have reviewed multiple factors which affect the telomerase activity and the length of the telomeres throughout the life span which include many genetic factors such as P13k/Akt signaling cascades, insulin resistance and tumor promoting genes etc. as well as the epigenetic factors such as the metabolic regulation through mitochondrial signaling, endoplasmic reticulum chronic stress and inflammatory diseases. The process of cellular senescence is amenable to molecular analysis and needs to determine the easily measured biological markers of ageing. Scientists believe that DNA chip arrays are very helpful to determine the gene expression of the entire genome which can provide the constructive biomarkers of cellular ageing. If the researchers are able to determine the characteristic pattern of changes in life span of the organism for example in nude mice, the DNA chip arrays will then be able to measure the rate of cellular senescence in genetically and physiologically transformed organisms. The genome analysis can also be an amiable indicators of relevant human polymorphic loci associated with cellular prolonged existence. Since, only limited key cascades are critical to control the cellular longevity, there must be specific molecular targets that work as therapeutic pharmacological interventions. Scientists have cloned the adult somatic cells which indicated that age related nuclear alterations may be reversible. These somatic cells that have been cloned may represent that they have fugitive age linked cellular events. In the past decade, the human life expectancy has been improved due to advances in therapeutic and medicinal approaches. The average life span is impacted probably to a small extent than that in the past two centuries. Slowing down the process of ageing increases the longevity and vitality of the organism over the whole life span. Of course, slowing down the ageing process faces many complex implications. Indeed, an over populated country, it is important to cut down the birth rates to achieve the significant effects on longevity and survival. Many industrialized countries have implicated this birth control strategy and have productive long lived individuals associated with improved health. The progress gradually depends on the increased knowledge and wisdom of the individuals to achieve premium benefits of organisms' longevity.

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AUTHOR CONTRIBUTIONS

Sara Zahid-Writing and designing the original draft; Fatima Zahid-Reviewing and editing; Faisal Gulzar-Supervision

DATA AVAILABILITY

All relevant data is included in this manuscript

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