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RECENT ADVANCEMENTS IN ANTI-AGEING THERAPEUTICS- A REVIEW

V. Devi Rajeswari*[1], Joel Armstrong[1], Atul Preetham[1], Sai Mithilesh[1], Kanagavalli Ramasubbu[1], Abbas Alam Choudhury[1], Rosmi Jos Menakapriya[1], B. Manosi Banerjee[1], Shreya Chakrborty[1]

[1*]Department of Biomedical Sciences, School of Biosciences and Technology, Vellore Institute of Technology, Vellore, Tamilnadu, India.

ABSTRACT

The term ageing is a ubiquitous biological phenomenon that leads to advancing and deleterious changes in organisms. For centuries mankind has worked tirelessly with the goal of prolonging or if possible, reversing this phenomenon. In recent times, owing to the development of biotechnology and modern therapeutics, there are many promising approaches towards prolonging ageing. One of them involves the usage of stem cell transplantation to depress the detrimental health effects of ageing. Studies showed that aged patients suffering from cardio-vascular diseases have gotten over their ailments upon receiving a single infusion of stem cells from donors who are in their pink of health. Klotho, a gene which was initially discerned as a presumptive anti-ageing gene in mice, has been found to extend the viability of the animal. It has been shown to produce composite phenotypes that resemble early ageing syndromes when there is a defect. Another approach involves Telomeres, an element of chromosomes, which play an important part in ageing as they are repetitive DNA sequences. Resveratrol an antioxidant polyphenols isolated from red wine has been found to possess anti-ageing properties.

KEYWORDS

Anti-Ageing, Stem cell transplantation, hMSC, Klotho gene, Telomeres and Resveratrol.

Author for Correspondence:

Devi Rajeswari V,
Department of Biomedical Sciences,
School of Biosciences and Technology,
Vellore Institute of Technology,
Vellore, Tamilnadu, India.

Email: sdevirajeswari@gmail.com

INTRODUCTON

Ageing is a rapid, pernicious and universal changes undergone by every living organism. Mankind has been obsessed with finding a cure for ageing over many centuries, often giving rise to many myths, across different cultures around the world. Recent advancements made in the field of anti-ageing therapeutics have given a fresh breath of life to humanity's long search for longevity.

With the research being done in this field, it has been accepted that ageing is a multifaceted event

that results from a collective effect of several factors such as genetic variation, nutritional factors and lifestyle[1]. With the obstrusion and iniquity of these factors, the human body undergoes massive deterioration in bodily functions and a gradual loss of homoeostasis. Frailty is among one of the most common problems of ageing and is defined by its symptoms of reduced motor functions, fortitude and musculature[2]. The gross ubiquity of the syndrome has been found out to be around 9.9%, mainly affecting women. It also affects those with a chronic disease. It's multifarious etiology often results in a shortened life span and greater dependency on other people for carrying out their daily tasks[3]. Any prospective treatment for the syndrome should revolve around the need to regenerate movement and workability. Among the many theories that surround ageing, one of the key hypotheses involves an increased exhaustion of stem cells that are endogenous and this leads to a reduction in the capacity to revitalize tissues[4].

Human mesenchymal stem cells (hMSCs), which are derived from the bone marrow, can be placed in sites of injury, and thereby reducing swelling and fibrosis, re-vitalizes endogenous stem cells, and plays an important role in tissue regeneration[5]. hMSCs through clinical studies have shown that there is an improvement in the structure of the cardiac muscles and it's performance in patients suffering from heart attacks. It also improves ischemic and non- ischemic heart failure and has been been found to be immunomodulatory in nature[3-7]. Many clinical trials that have been under taken also show that allogenic hMSCs are safe regardless of age. Thus, it can be concluded that these features of hMSCs help in improving those suffering from frailty. Klotho, a gene that codes for proteins that are characterised by the presence of a single transmembrane domain, is manifested predominantly in the kidney, in renal tubules. A flawin the expression of the gene results in a syndrome resembling premature ageing, while on the other hand, over expression leads to an increase in life span[8,9]. Telomeres, which are repetitive elements of DNA that are non-coding, present at the nibs of chromosomes with capped ends with a sequence of single and double stranded DNA binding proteins, have been found to play a vital role in the ageing process.

The reduction in the length of telomeres in cells during cell division, which mainly occurs in the rapid proliferation of cells of the skin, gastrointestinal organs and blood, have been found to trigger cell senescence after a certain shortened length of the telomere has been reached. The cell senescence leads to changes in the homeostasis of the tissue which result in ageing[1]. Resveratrol, an antioxidant polyphenol isolated from red wine, has been the subject of intensive investigation of late. It is a very potent antioxidant and a modulator for the expression of genes through signal transduction. It also inhibits inflammatory mediators and possesses phyto-hormonal properties. This distinctive mixture of biological characters and outward effects, make Resveratrol a good candidate for being an anti-ageing agent[10].

STEM CELLS

The process of ageing involves many factors such as genetic, non-genetic and environmental, whose message accumulate in vital stem cells which are coordinated by a second set of vital life elongating genes. This shows that all phenomena associated with ageing could be based on stem cells. Stem cells have the ability to magnify the recuperative ability of living organisms. Hence, stem cells are a central factor in determining ageing[11].

hMSC and Ageing

Mesenchymal stem cells (MSCs) are often used for the development of cell therapies in the field of regenerative medicine. The stem cell pool in adults assure in the preservation and regulation of adult tissues and organs. The MSCs have transpired to become prospective candidates for therapy based on cells, in numerous diseases. hMSCs are self renewing and are competent in multi lineage differentiation into a variety of tissues which originate from the mesoderm. They are non-hematopoetic cells[12]. The stroma of almost every organ, allows it's isolation and expansion, albeit the sources that are often preferred include subcutaneous fat and bone marrow[13]. hMSCs, upon isolation are distinguished by their ability to cohere to plastic and subsequently grow into fibroblast CFUs. This is followed by its differentiation into

cells such as adipocytes, chondrocytes and osteocytes[14].

Aside from their powerful ability to differentiate, they have an extraordinary capacity to impede the immune response, a process referred to as immunoregulation[15].

The immunomodulatory ability of hMSCs include the growth and inhibition of B and T cells. It also has the ability to inhibit the production of cytokines along with a lowered operation of NK cells. These features have proven to be advantageous for their use in experimental models of autoimmune and inflammation disorder treatment. They have also been used for prevention of allogeneic transplant rejection.

The benefits of hMSC based cell therapy involves the wide repertory of the trophic factors that are secreted. These secretions are called the MSC secretome. They showcase a wide variety of functions that include immunoregulation, anti-apoptotic and anti-inflammatory activity. It also regulates angiogenesis. Their growth potential is high along with increased multipotency and paracrine effect[16,17]. hMSCs once cultured, undergo a restricted number of divisions, which is a process referred to as cellular senescence[18]. Due to the scarcity of hMSCs in the body, millions of cells are required per procedure in cell therapeutic protocols, and there is a subsequent need for expansion of these cells in vitro for a ten week period prior to implantation. The quality and time period for the cells and their expansion is highly dependent on the age, genetic makeup and clinical history of the patient[19,20]. It has been found that younger MSCs perform better than their older counterparts[21]. This has increased substantiation that suggests the contribution of cellular senescence to towards ageing and age related disorders. The secretions of senescent cells affect core and compactly modulated processes, which includes growth and migration of the cell, angiogenesis, differentiation and tissue design. One of the primary attributes of ageing is chronic inflammation and has been found to be the reason behind the commencement of a majority of gerontic disorders. The production of powerful oxidants and other factors by certain immunocytes can result in negatively affecting cell and tissue quality and this often leads to subsequent alteration and remodelling of the tissue environment, thereby advancing tissue dysfunction and stem cell deterioration[22-24].

hMSC and Cardiomyopathy

The use of allogeneic MSCs in cardio-vascular medicine, has shown much promise in recent years, as it has been used to treat ischemic and non-ischemic cardiomyopathy.

Many clinical studies have noted that MSC based therapy being employed in cardiomyopathy treatment has led to the reduction of fibrosis of the cardiac tissue, stimulates the formation of new blood vessels and has enhanced the function of remodelled ventricles. Through genetic modification and preconditioning the cell, many attempts have been made to extend the effect of MSCs. The improvements in cardiac structure and function, along with patient quality of life and functional capacity has been supported by the developments made in MSC therapy by conducting speedy clinical trials. The need for larger clinical trials has been supported by the newly emergent data from existing trials that are underway or have been completed[25,26].

Clinical Trials

Lowered physiological reserves which leads to the individual developing morbidity or mortality, or both, are symptoms of frailty. The general treatment that is given for frailty have primarily focussed on exercise, food and nutrition, pharmacologic drugs or a combination of all these factors. The CRATUS trial, one of the pioneering clinical trials that were conducted, had hypothesised that allogenic hMSCs were safe and effective for treating ageing frailty syndrome. The study aimed to intravenously infuse hMSCs into patients with the syndrome and compare the phenotypic outcomes[27]. It was later concluded that allo- hMSCs are safe and were histochemically supported in ageing frailty patients[28].

KLOTHO GENE

A gene in a certain mouse strain which was inherited in an autosomal recessive mode, upon disruption resulted in a syndrome that resembled human ageing, was initially identified. This was called the Klotho gene[29]. The protein, Klotho has three domains: A 130kD large domain that is

extracellular, a small intracellular domain made of ten amino acids and a transmembrane domain. The large extracellular domain is released in the blood and the urine by process of ectodomain shedding. The protein has two distinct forms, a membrane Klotho and a secreted Klotho, each with it's unique set of functions.

Klotho and FGF23

A fibroblast growth factor (FGF) receptor forms a composite with membrane Klotho. This leads to it's function as an obligate co-receptor of FGF23, a hormone that is derived from bone tissue, and this rouses the excretion of phosphate into urine. Research has shown that mice that lacked FGF23 or Klotho protein displayed an early ageing syndrome. The function of the secreted Klotho involves it being a humoral factor, which controls multiple glycoprotein activity on the cell surface, along with ion channels. It also controls the activity of insulin and insulin like growth factor-1, which are growth factor receptors. These factors together contribute to the ageing process[30-32].

Until it was discovered that mice deficient in Klotho and FGF23, displayed similar phenotypes, the purpose of membrane Klotho was unknown. FGF23's function was only recognised after it became clear that it was the mutated gene that was found in patients with a version of hypophosphatemic rickets that was autosomal dominant, also called ADHR. This disorder was distinguished due to hypophosphatemia by phosphate being wasted away into urine, extremely low levels of calcitriol in serum and also rickets[33]. Mice that were found to be deficient in FGF23, were distressed by phenotypes of phosphate retention and this often included hyperphosphatemia and clacification of vascular tissue[34]. Aside from these predicted phenotypes, mice that were deficient in FGF23 also abruptly developed complex phenotypes that were similar to that of ageing. This included symptoms such as arrested growth, atrophy of various organs, excessive convex curvature of the spine (kyphosis) and osteopenia[35]. Inversely, mice that were deficient in the Klotho gene, exhibited hypophosphatemia and calcification of the vascular tissue like those seen in mice deficient in FGF[23,29,36,37]. This discovery led to the hypothesis that the Klotho gene and FGF23 may have the same pathway of signal transduction.

It was discovered that FGF23 required membrane Klotho for binding to related FGF receptors[38,39]. Despite FGF23 belonging in the FGF family, it is unable to bind with the FGFR with a high degree of affinity. However, a composite of Klotho- FGFR is used as the high-affinity receptor by FGF23. Thus it can be concluded that Klotho is an obligate co-receptor of FGF23 and the development of identical phenotypes in mice that lack FGF23 and Klotho, is due to this. Moreover, Klotho being expressed in nephritic-specific cells, is a good explanation for the hormone FGF23 targetting the kidney as a target site, despite there being other tissues that showcase different isoforms of FGFR. The disorders of ageing due to flaws in the FGF-Klotho system which include hypervitaminosis D and hyperphosphatemia that are associated with mice without Klotho or FGF23 can be linked to retention of phosphate and ergocalciferol intoxication. While many laboratories have opted for resolving hyperphosphatemia and hypervitaminosis D through nourishment and genetic intercession, it has been observed that a diet lacking in vitamin D, saved many mice with phenotypes of ageing, like those without Klotho and FGF23 experience[36,40]. Likewise a disturbance in the gene for vitamin D receptor (VDR) or the gene Cyp27b1, which codes for 1a-hydroxylase, an important enzyme in the synthesis of calcitriol, has been found to save these mice with mutations. Through this we are able to conclude that ergocalciferol activity might be the cause for the showcasing of phenotypes of ageing[35,41,42]. It has been observed that by restricting reabsorption of phosphate through deletion of the gene coding for Npt2a, results in the reduction of the levels of phosphate in the blood, even though serum calcium and calcitriol are not brought down to normal levels[43]. Thus it was seen that these observations stipulated that retention of phosphate lead to phenotypes that resembled ageing, and this is broadly referred to as phosphatopathies.

TELOMERS

Organismal ageing is a complex phenomenon. One such theory developed by scientists to explain the phenotypes of ageing is the telomere theory.

Although it can't explain all the phenomenon and proceedings involved in the ageing process, it throws some light on the idea of reduction in telomere length being involved in some countenance of human ageing. Moreover, usage of the enzyme telomerase for tissue engineering provide a future perspective in the research field of developmental and regenerative medicine[44]. DNA sequences at the ends of chromosomes are known as telomeres. They are repetitive sequences of DNA. In humans, the enzyme; a reverse transcriptase by the name of telomerases help preserve the length of telomeres. Telomerases are present in the stem cells and reproductive cells. They maintain the length by the addition of TTAGGG towards the end of telomeres. Most somatic cells don't showcase these enzymes and as a result, due to recurring cellular division, a part of the telomeric sequence is lost. Once telomeres reach a limiting length, the whole cell enters into a plight called replicative senescence. At this stage, the cells exhibit a non-reversible growth arrest. It is argued that it is because of the induction of anti-proliferative signals, that the arrest takes place[45]. Earlier, there were theories and assumptions that the cells in the human body had the capability to propagate forever. A scientist by the name of Leonard Hayflick brought aradical change in this particular field of study and an end to the previous notions and arguments. Hayflick experimented with fibroblast present in the human body and figured out that these isolated fibroblasts had only a finite capability to propagate. The had a limited number of growth cycles and the cells that have arrived at the limiting number of divisions ceased to proliferate[46]. Post the limiting number of divisions, the cells became senescent. These cells had particular descriptions such that they are usually flat and extended. Even though they had lost the ability to divide, they were found to be metabolically active.

This research then made way to the conclusions; cells had a check on the cycles of division it had gone through by means of a clocking mechanism and that this particular mechanism had the capability to cut off any further divisions from the limiting number of divisions. The number of divisions a particular cell is allowed to undergo is named after Leonard himself as the "Hayflick's limit".

Telomere hypothesis

Scientists Watson and Olovnikov[46,47] put forward the notion that chromosomes are incapable of copying the 3' end dependably even if provided with a RNA primer at the furthermost end. Despite everything, a small part of the chromosome would not be copied. This can be fatal if there were genetic information located in this part. Nature itself has provided a solution for this intrinsic problem by the introduction of the telomere. As stated earlier, they are repeats of TTAGGG (particularly in mammals). They are non-coding as well.

Scientists Harley and Greider, along with their colleagues began observing telomeres after DNA replication was conducted for several cycles[49]. In order to conduct this experiment, they had to make use of restriction enzymes that cut only the chromosomal DNA and not identify the repetitive hexanucleotide sequences of telomeres. The dimensions of telomeres from sequential divisions were gathered by analysis using Southern Blot. Through their experiment, they were able to find out that the average length of telomere was getting reduced successively as the division cycle passed on. This was in par with the prediction of both Watson and Olovnikov. Another set of observations from their experiment was that the cells from same source when cultured separately provided more or less the same telomeric length[50]. This points in the direction of the research conducted by Hayflick regarding the clock mechanism employed by telomeres for ageing phenomenon. Once the Hayflick limit was achieved, it is the responsibility of DNA sequences to trigger the entry of cell to senescence stage.

From the above-mentioned arguments and experimental facts, we can conclude that the lifespan of cells is controlled by telomeres. The structural maintenance of telomeres is the eciding factor in cellular replication.

Cell Senescence and Ageing

As stated above, somatic cells undergo only a finite number of cell cycles before senescence stage is initiated[48,51]. Because of this limited capability, there are proposals that this is the reason for changes that comes along with ageing namely

degenerate wound healing capabilities and weak immunity[52]. Diseases like AIDS and cirrhosis are moderately due to limited capability of tissue regeneration. The relation between ageing and senescence is backed by the correlation between age of donor and length of telomere[53]. It is also backed up by reduced propagation of cells which were isolated from individuals who suffer from diseases which have premature aging as their main characterization. This reduction is with comparison to normal cells whose ages are matched[54]. A particular thing is to look into people who grieve from the disease known as dyskeratosis congenita[55]. This particular disease exists in two forms, a form that is autosomalrecessive and is a product of mutated TERC gene. The TERC gene is responsible for the telomerase as it codes for its RNA subunit. The other is an autosomal dominant form. This is a sex linked one with linkage to the X chromosome. This is a result of dyskerin gene mutation. This particular gene in a way, affect telomerase assembly rendering function loss of the enzyme[56]. Upon scrutinizing the situation of the patients, it confirms the shortening of telomers in comparison to age matched cells. Anticipation is also exhibited in these patients. By anticipation, we mean that the intensity of symptoms increases with each generation. These symptoms exhibited are also similar to those of aged humans as well. Thus, different aspects of ageing is phenocopied by small faults in the preservation of telomeres. However, this does not provide proof that telomere length is the main cause of human ageing[57].

Biomarker of Ageing

Telomeres also supposedly act as an ageing biomarker. Biomarkers are said to provide information regarding a person's health and his/her status of function than the mere age mark[58]. Biomarkers can also be regarded as a parameter and is useful for identification of personnel suffering from diseases. The fact that the length of the telomere gets reduced as a person ages is the reason why telomeres are selected to be a biomarker. There are many instances that identify an inverse relation between the length of telomere and age-related issues such as sensitive measures and abnormalities. Scientists Martin- Ruiz and von Zglinicki figured that telomeres checked the box for different criteria needed for a biomarker of ageing. This is because it changes with age, variability between individuals is high and relates well with aging and diseases associated with ageing.

RESVERATROL

Resveratol is a unique compound with very specific properties that serve in its ability to combat aging. It can be isolated from red wine using liquid extraction and further optimized by response surface methodology[59]. Another method involves reflux extraction, filtering, hydrolyzing, liquid–liquid extraction and eluting of Polygonum Cuspidatum, a traditional medicine from which resveratrol can be extracted[60]. The high potency of antioxidativeness of resveratrol, ability to modulate the expression of genes via signal transduction, capacity to inhibit mediators of inflammation and other properties such as sirutin mimetics and induction of phyto-hormonal effects make resveratrol a very promising and significant compound in development of anti aging therapeutics[61].

Anti-oxidative Property

Reactive Oxygen Species (ROS) refers to the term used to define the oxygen-centered radicals non radicals which are by-products consequent of continuous normal everyday metabolic activities of the human mammalian metabolism. Multiple exogenous determinants that include UV radiation exposure, herbicide compounds and air pollutants directly or indirectly affect the increase in production of ROS. ROS evokes a negative effect on the biomolecules of the human system thus modulating the normal functioning of the cell. Over the years ROS accumulates in the body causing aging, inducing senescence and other negative effects including necrosis and apoptosis[62]. To counter the adverse effects of ROS, inherent antioxidant systems in the human body. However owing to excessive ROS generation paired with weakened antioxidant systems over time, an imbalance occurs between this redox system leading to the development of a condition known as oxidative stress. Oxidative stress is a harmful tissue damaging mechanism that causes deleterious changes in the human body[63]. Strong inhibition in ROS which is induced by formylmethionyl leucyl

phenyalanine (fMLP) in polymorphonuclear leukocytes is seen with the interference of resveratrol[64]. Resveratrol can specifically act on targets in blood cells and in globular proteins. Following incubation with plasma, globular proteins and cells resveratrol was successfully incorporated into these cells[65]. Hence, owing to its lipophilic characteristics, resveratrol is able to bind the globular protein particles suggesting that this binding phenomena induced improved antioxidant activity of lipoproteins[66]. Lipids are characteristic parts of cellular membranes and take the role of steroid hormones and retinoic acids. Studies have shown that lipid peroxidation negatively impacts biomembranes including disturbing the fine structures, altering their permeability and hence causing loss of function, along with generation of potentially toxic products[66]. Lipid peroxidation leads to products that tend to be to be carcinogens and mutagens and has been discovered as one of the chief causes aiding in the development of various disorders and diseases which include neurological, cardio-vascular, cancer and also aging[67]. After resveratrol-rich intake there has been a measurable improvement in the antioxidative capacity of the plasma and consequent decreased globular peroxidation[68]. It was shown that resveratrol possess the ability to inhibit lipid peroxidation and intracellular oxidation in common yeast strains. The results of the study conducted by Dani *et al*, showed that after resveratrol incubation, the levels of ROS produced in yeast reduced by 3-folds, suggesting that resveratrol has the ability to eliminate peroxide radicals[69]. Resveratrol also along with being a potent antioxidant also protects proteins from oxidation. As shown by Pandey *et al*. Resveratrol protected and hence prevented oxidative stress disruption in the development of protein carbonyls embedded on the cellular membrane of RBCs and plasma under the condition of oxidative stress[70]. To counteract the adverse effects of oxidative stress and ROS the cellular components of living bodies consist of various antioxidant systems which include superoxide dismutase, non-enzymatic antioxidants such as reduced glutathione (GSH) and uric acid. Various studies have shown that resveratrol significantly improves the activity of these antioxidant systems. GSH is an important intracellular non-protein compound and it is one the most significant water soluble antioxidants. Yen *et al*, showed that resveratrol at concentrations of 10–100μM counteracts and inhibits the effects of H2O2 induced oxidative injury by means of increased GSH levels[71]. This phenomena is further supported by the results of the study by which confirms that an increase in production of GSH is a direct result of to the free radical affinity of resveratrol[72].

Sirtuin Mimetics

Longevity of life can be promoted using a mechanism known as caloric restriction. It involves the activation of sirtuins, a histone deacetylase enzyme. These enzymes further alter the metabolism of the mitochondria, increase insulin sensitivity, lower levels of insulin-like growth factor-1, increase AMP-activated protein kinase. Wine polyphenols including resveratol are important functional compounds and sirtuin mimetics with the capability of replication of the calorie restriction effect by means of sirtuin production and activity up-regulation[61]. According to a study conducted by Baur *et al*, resveratrol effectively extends the life span of mice with a diet consisting of high calorie intake. This means that the mice in their middle ages with a high calorie intake shows a shift in their physiology to a standard diet and thus consequently increase its life span. In the presence of resveratrol the mice showed increased insulin sensitivity, decreased organ pathology, increased mitochondria and hence had prolonged ages due to caloric restriction[73].

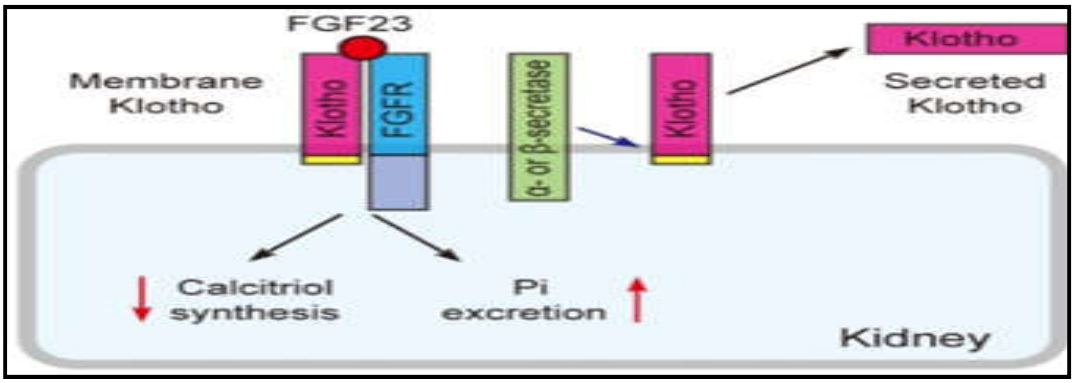

Illustration No.1: Membrane Klotho and secreted Klotho. A complex is formed with FGFR by the Membrane Klotho, which creates a new binding site for FGF23. By subjecting Membrane Klotho to the α- and β-secretases, it undergoes ectodomain shedding to release secreted Klotho[32]

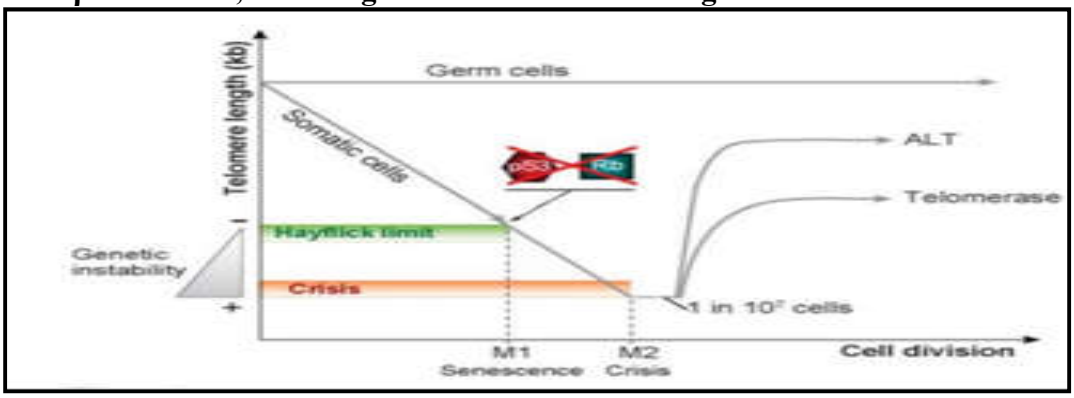

Illustration No.2: The telomere hypothesis. The length of the telomere (ordinate) is reduced with each round of cell division, eventually leading to senescence. The in activation of the functions p53 and Rb, signals continued cellular division and this results in telomere shortening. The telomere eventually erodes to a length beyond which, the chromosome ends remain unprotected, resulting in fusion of the ends of the telomers and cell death[48]

CONCLUSION

Ageing is a cause for much anxiety in most people. Throughout the centuries mankind has tried to seek out a cure to ageing. While no one single such cure exists, through our discussion so far, we have seen that through all these research that has been done over the years, that there is an extremely high chance of being able to lengthen one's lifespan. With the knowledge that we have accumulated about stem cells, we now know that it is viable to use them for designing tests and interventions that could slow down the process of ageing and thereby upgrade one's health and increase longevity. By using anti-ageing genes such as Klotho in conjugation with stem cells, a protective shield can be formed that helps the body withstand against the degrading effects if ageing. It has been observed that by up regulating the activity of the telomerase enzyme, life span of cells can be greatly lengthened and the limiting number of cell divisions possible can be overcome[74]. It has also been proposed that telomer length can be used as a biomarker for ageing as evidence suggests that it meets the required criterion[58]. Due to the extremely potent and unique range of anti-ageing properties, the anti-oxidant polyphenol Resveratrol has further opened the doors towards exploring what lies ahead in anti-ageing treatment. The many benefits of Resveratrol such as its anti-cancer, anti- microbial and sirtuin activation has made it a front runner in the anti-ageing therapeutics[61]. Anti-Ageing therapeutics is still in its infancy, but from what we have seen so far, it is clear that in the future we will be able to see a world where we can reverse ageing and letman kind become younger and healthier.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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