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Genetic Engineering: A Panacea to Senescense and Death

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Abstract: Senescence (aging) has a great impact in diseases and life expectancy of living organisms. Recent developments in genetic engineering and scientific understanding of the flaws of human, plant and animal bodiesportend a great stride towards achieving immortality. With current knowledge of genome editing technology such as clustered regularly interspaced short palindromic repeat (CRISPR), telomere engineering and stem cells manipulation, it is possible to design and test interventions that delay aging and improve both health and lifespan. These technologies have the ability to insert or delete, activate or deactivate and reset the genotype orphenotype of individuals, thereby, delaying aging and its adverse effects.Rejuvenation of cells through the control of apoptosis, treatment of genetic disorders through gene therapyand neutralization of devastating signaling pathway through the regulation of metabolites or gene expression have been achieved through these technologies. If factors such as proliferation of cells and other ethical issues are tackled, it is believed that living organisms can live younger and longer than expected and immortality could be achieved in nearest future.

Key words: Aging · CRISPR · Disease · Gene · Immortality · Technology

INTRODUCTION

All living organismspossess several characteristics, namely; movement, respiration, nutrition, irritability, growth, excretion and reproduction. These anabolic and catabolicprocesses result in changes in cellular anatomical, physiological and biochemical fates. During these processes, cells as fundamental unit of life are being generated, degenerated or weakened or aged until they cease to exist. The cells undergo apoptotic and necrotic processes which the end may be irreversible, thus, death.The reversibilityof aging may be another biological theory that scientific advances will achieve in the near future. A number of scientists assert that longevity is a societal concept that does not need to be upheld as a static law of nature, but as one that can be modified to our benefit [1]. Researchers across the field of genetics to artificial intelligence (AI) have prospect of a future where "midlife crisis" would not be used to justify our ill-advised decisions while there have been numerous theoretical ideas and initiatives for ducking the Grim Reaper [1].

During the last century, many dramatic discoveries were made and with the advent of genetic engineering, great strides exist in the improvement of various organisms, coupled with the understanding of senescence (aging) and deathin the world today. It is believed that the problem of aging and death can be tackled at cellular level (through the genes), although many evolutionary biologists would deny that aging is part of the genetic repertoire of a living organism (humans, animals or plants) [2]. Rather, they would consider aging to be the default state occurring after the organism has fulfilled the requirements of natural selection. After their offspring are born and raised, the organism can die. This is exactly what happens in many organisms such as moths and salmon; as soon as the fertilized eggs are laid, the adults die.Nevertheless, recent studies have shown that there are genetic components to senescence and that the genetically determined life span characteristic of a species can be modulated by altering genes [3]. This modification can occur in plants, animals and humans' gene in the process known as *Genetic Engineering*.

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According to Britannica.com, genetic engineering involves various techniques used for the manipulationor modification of organisms through the processes of reproduction and heredity. It includes both artificial selection and biomedical techniques, such as in-vitro fertilization, artificial insemination and cloning. In the 20th century, genetic engineering referred more specifically to methods of recombinant DNA technologyin which DNA molecules from two or more organisms are joined either within or outside cellsand then inserted into host organisms for propagation.Genetic engineering could conceivably fix extreme genetic disorders in people by supplanting the faulty gene with a working one. It is an essential instrument in research that enables the capacity of particular gene to be analyzed.

Genetic engineering methods involving use of gene editing (CRISPR technology) combined with other gene therapy methods involving insertion of modified DNA strands or genes e.g. fusion of Tet1 (Ten-eleven translocation methylcytosinedioxygenase 1)or DNMT3A (DNA Methyltransferase 3 Alpha)with a catalytically inactive Cas9 (dCas9) enables targeted DNA methylation editing [4]. BER (Base Excision Repair) introduced into the cell repairs most of the oxidized DNA damage [5]. Overexpression of heat shock protein 70 (HSP70) also protects against age and disease related tissue degeneration in brain, heart and skeletal muscle [6].

Researchers have taken a particular enthusiasm for aging and consequent death. New technological leaps have shown capacity to direct a closer investigation into possible prevention of senescence and natural deaths in living organisms. With the advances in different genetic engineering methods, scientists have estimated that senescence and death would be a thing of the past by the year, 2050 [7]. Growth and development of organisms are accompanied by generation anddegeneration (necrotic or apoptotic) of cells. As the process prolongs, the organism begins to age, which is a major factor that leads to certain diseases such as senile dementia, poor sight, reduced physical activities and sudden death. Studies have demonstrated that senescence can be controlled, by genetic variables and biological procedures inherent to humankind through genetic engineering. It is believed that the pathological and programmed cell death could be controlled through the manipulation of specific genes in the genome of any organism involved. Once the cause of diseases (genetic and non-genetic) are controlled or prevented and cells genetically manipulated for longevity, natural death can be reduced if not averted.

Understanding Senescence and Death: Senescence is synonymous with aging.It occurs virtually in all living organisms ranging from eukaryotes to prokaryotes. Any multicellular organism utilizing energy from the sun can develop and maintain itself; progressively, the synthesized products gradually degenerates and the organism ages. Aging is the time-related decay of the physiological capacities necessary for fertilityand survival. Its qualities influence every one of the people of a species.Senescence is a cellular program that causes a reliable growth arrest combined with unmistakable phenotypic alterations, extending from chromatin redesigning to metabolic reconstructing, extended autophagy and the execution of a complex proinflammatory secretome [8, 9]. These unpredictable changes to the cell, as it were, serve to realize distinctive parts of senescence, for instance, growth arrest and the senescence secretome. Notwithstanding the various signs of senescence, stable development arrest is its portraying trademark. An invariable arrest is feasible to ensure that harmed or transformed cells do not propagate their genomes. This development arrest is executed by the actuation of p16INK4a-Rb and p53-p21Cip1 tumor silencer systems [10]. Senescence is without a doubt an incredible instrument of tumor concealment [11, 12]. Senescence has in like manner physiological functions in the midst of standard enhancement [13, 14], cooperating with apoptosis to empower embryonic morphogenesis. In grown-up tissues, senescence is actuated primarily as a response to harm, mulling over camouflage of potentially broken, transformed, or developed cells. In spite of the way that senescence is a normally indispensable process, it may incorporate some noteworthy destruction.

In mammals, senescence (aging) occurs across multiple organ systems, inducing progressive deterioration that may result in tissue dysfunction. Therefore, aging is a risk factor for many diseases [15], such as cardiovascular disease, dementia, osteoporosis, osteoarthritis, cancer, type 2 diabetes, idiopathic pulmonary fibrosis and glaucoma [16-18]. Our understanding of the aging process remains limited irrespective of these links with human pathology. Although thefull biological causes of aging is yet unknown, previous studies have identified common cellular and molecular traits associated with it [19].

Plant senescence is the recycling of plant's valuable cellular building blocks deposited in the leaves and other parts in the midst of advancement [20]. These recyclable

nutrients can be used in new advancement or development of the plant or sent to the seed as supplement store to the next generation. Senescence in plantsis therefore fundamental for their wellbeing. It is a complex and coordinated process that involvesthe interactions of many signaling pathways resulting inthe expression of new qualities. In harvests, inappropriately timed senescence can decrease final product yield and in various vegetable yields, basic postharvest hardship is a result of senescence. Unraveling the managerial parts that underlie senescence may have significant impact on extending future sustenance generation.

In *prokaryotic cells* such as bacteria, the cells do not have a fixed life span but the parent cells divide to produce the new cells. The new ones do not divide immediately, rather, they grow and develop within very short periods before they divide. This period of growth is accompanied with senescence.

Numerous evolutionary scholars would deny that senescence or aging is a piece of the genetic collection of a cell or an organism, or they may view aging as the default state happening after the cell or organism has satisfied the necessities of natural selection [2]. After its posterity are brought up, the cell or organism can die. In fact, in numerous organisms, from moths to salmon, this is actually what occurs. When the eggs are fertilized and laid, the grown-ups die. It is the progressive deterioration of living things that ultimately leads to its death. Late examinations have shown that there are genetic parts to senescence and that the genetically decided life expectancy normal for a species can be regulated by adjusting genes or diet. In humans, aging is the long time accumulated assembly of physical, mental and social changes. Aging is among the most elevated realized hazard factors for most human diseases of the approximately 150,000 individuals who die every day over the globe, around 66% pass on from age-related causes [21].

Death is the cessation of the fundamental biological activities that sustain a living organism. It can occur at cell, tissue, organ, system or whole organism levels. At cell or tissue levels, death can be programmed (apoptosis) or pathological (necrosis) [22] and thus, reversible but at the whole organism level, death is irreversible. It could be caused by various factors, such asaging, predation, malnutrition, disease, starvationand accidents or major trauma resulting in terminal injury [23].

Negligible Senescence and Immortality: Virtually, all living organisms are prone to senescence and death but there are certain species of living organisms or their cells that may not age or die. This is seen as negligible senescence and death observed in both microorganisms, plants and animals. Although most microorganisms such as fungi age, numerous species can be viewed as immortal: for example, bacteria dividebetween once every 12 minutes and 24 hours to deliver daughter cells with a life span of about 250 million years [24]. Some perennial plants ranging from strawberries, potatoes to willow trees undergo vegetative propagation and are seen as potentially undying. Hydra avoids death by aging through its regenerative capacity. The 15,000-year-old Antarctic sponges known as the most seasoned animals can recreate both sexually and clonally. Asides clonal immortality, there are a few species whose singular life expectancies standout amongst other Earth's animals, e.g. the bristlecone pine at 5062 years or 5067 years, likewise invertebrates, for example, the hard clam otherwise called quahog in New England at 508 years, the Greenland shark at 400 years, different deep sea tube worms at more than 300 years, fishes, for example, the sturgeon and rockfish, more so sea anemones and lobsters. Such organisms are now and then said to display negligible senescence [25].

Early living things (prokaryotes, protozoans, algae) on Earth, beginning in any event 3.7 billion years prior were unicellular organisms. Theymultiplied by fission into daughter cells. Consequently, they do not age and are biologically (innately) immortal [26]. Aging and mortality of organisms at that point ended up conceivable with the change (advancement) of sexual propagation which happened with the outgrowth of the fungal/animal kingdoms around a billion years back and the development of seed creating plants around 320 million years earlier.

Certainly, even inside humans and mortal species, there are cells with the potential for immortality: cancer cells which have lost the capacity to die when kept up in a cell culture, for example, the HeLa cell line and particular undifferentiated cells, for example, germ cells (creating ova and spermatozoa). Grown-up cells can be restored to embryonic status in artificial cloningand then be used to grow another tissue without aging. According to Hayflick and Moorhead [27], a typical human cell normally die after about 40-60 cell divisions in laboratory culture.

Causes of Senescence (Cellular Death): Evidences abound on the causes of senescence in different species of living organisms, although, there is no consensus. Various factors such as DNA repair, oxidative stress,unfolded protein response, stem cell exhaustion, genetic aging programs, mitochondrial genome damage and telomere shortening have been attributed to be the major causes of senescence at different cellular level of organization. Other factors that contribute to aging include: glycation, stress and inflammation [28].

DNA Repair: DNA repair system plays a part in the aging process. During replication, DNA is modified and a control system uses proteins and enzymes to reprogram the modified cell.In the cause of modifying the damaged DNA, these proteins exert other effects that are linked tomitochondrial functions andnicotinamide adenine dinucleotide (NAD+)[29]. Studies have shown that more DNA-repairing proteins (PARP) can be found in aged individuals [30]. Over-activation of PARP leads to the exhaustion of NAD+ stocks and can induce cell apoptosisif the DNA damage is severe [31]. Aging is marked with an increase in the number of dead cells which leads to the degradation of organs.

Oxidative Damage: Oxidation is caused by free radicals that come from the oxygen contained in the air we breathe [30]. About 2-3% of the oxygen atoms taken up by the mitochondria are reduced insufficiently to reactive oxygen species(ROS) such as superoxide ion, the hydroxyl radical and hydrogen peroxide. ROS can oxidize and damage cell membranes, nucleic acids and proteins. Evidence for this theory includes the observation that Drosophila that overexpress enzymes (catalase) that destroy reactive oxygen species live 30-40% longer. Flies with mutations in the methuselah gene live 35% longer than wild-type flies. The methuselah mutants have enhanced resistance to paraquat, a poison that works by generating reactive oxygen species within cells [32]. Conversely, it has been shown that an increase in antioxidants has no effect on life expectancy, but an increase in the levels of free radicals result to longer life expectancy [33].

Unfolded Protein Response: Each protein has a specific unfolded shape (a linear chain of amino acids) in which it is not functional. The chemical properties of each amino acids gives protein its shape that enables it to perform its function within the cell. Many age-related diseases, especially neuro-degenerative diseases (Alzheimer and Parkinson disease) occur due to the buildup of unfolded proteins inside the cell [34].

Stem Cell Exhaustion: Stem cells: Stem cells are undifferentiated cells; they belong to no specific organ and can generate specialized cells through cellular differentiation. They are stored in the body and allow the renewal of cells in an organ. Some cells age and dieand need to be replaced on a regular basis. A red blood cell lasts for an average of 120 days. With aging, regeneration of tissues is affected due to the slowdown of cell division and the lack of stem cells replacement. This is shown by the accumulation of DNA damage on stem cells or overexpression of proteins blocking the cellular cycle [35, 36]. Some organs such as pancreas and heartcannot be renewed when damaged because they have no stem cells.

Genetic Aging Programs: Several genes have been implicated in aging. In humans, Hutchinson-Gilford progeria syndrome causes children to age fast and to die as early as 12 years usually due to heart failure. This is caused by a dominant mutant gene and its symptoms include thin skin with age spots, hair loss, arteriosclerosis and resorbed bone mass. Also, mutation of the klotho gene in mice causes similar syndrome [37]. The functions of the products of these genes are not known, but they are thought to be involved in suppressing the aging phenotypes. These proteins may be extremely important in determining the timing of senescence.

Mitochondrial Genome Damage: Degradation could be induced by the bridge of communication between the mitochondria and nucleus**.** The mutation rate in mitochondria is 10-20 times faster than the nuclear DNA mutation rate. It is thought that mutations in mitochondria could lead to defects in energy production, production of ROS by faulty electron transport and induce apoptosis. A recent report shows that there are “hot spots” for age-related mutations in the mitochondrial genome and that mitochondria with these mutations have a higher replication frequency than wild-type mitochondria [38]. Thus, the mutants are able to outcompete the wild-type mitochondria and eventually dominate the cell and its progeny. Moreover, the mutations may not only allow more ROS to be made, but may make the mitochondrial DNA more susceptible to ROS-mediated damage.

Telomere Shortening: Telomeres are repeated DNA sequences at the ends of chromosomes. They are not replicated by DNA polymerase and will shorten at each cell division unless maintained by telomerase. Telomerase adds the telomere onto the chromosome at each cell

division. It has been proposed that telomere shorteningcould be seen as a biological clock which activates cell senescence as soon as its time is up [30]. This limits the life expectancy of our cells. Genetic modification of old and weak mice in order to activate the genes responsible for telomerase production showed that the mice were rejuvenated and damaged tissue also regenerated [39]. Cultivated skin cells can divide about 40 to 60 times in their lifetime before beginning their aging process. Activation of telomerase production through genetic modification could lead to those cells dividing 300 times. However, increasing telomerase activity is linked with cancer.

Genetic Engineering Prospectsto Senescence and Death: The identification of various factors that lead to cell degeneration due to apoptotic or necrotic body activities and consequent aging or death is the first step towards finding their solutions. Advances in modern biotechnology has evolved some genetic engineering techniques that serve as preventive, curative and control measures to senescence, diseases and natural death in living organisms.Some of these techniques are discussed as follows;

Use of CRISPR-Cas9 System: According to Vidyasagar [40], CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) are specialized stretches of DNA while the Cas9 protein (CRISPR associated 9 protein) is an enzyme that acts like a pair of molecular scissors, capable of cutting strands of DNA. It is a powerful tool for editing thegenome of organisms that allows genetistics and researchers to alter the DNA sequences and modifythe functions of genes. It was developed from the natural defense mechanism of bacteria and archea. These organisms use CRISPR-derived RNA and Cas9 to foil attacks by viruses and other foreign bodies through cutting off and destroying of the DNA of foreign invaders. When these components are transferred into complex organisms, it allows for the editing of genes. The key advance in editing an organism's genome is particular targeting of a specific sequence of DNA. The communication of a complex of two biological macromolecules, the Cas9 protein and guide RNA, helps to distinguish target sequences with high selectivity. Both in natural and artificial CRISPR/Cas frameworks, the Cas9 protein finds and cleaves target DNA. It has six areas, REC I, REC II, PAM Interacting,RuvC, Bridge Helix and HNH [41].

This has generated huge fervor and extraordinary assumptions regarding the prospect of utilizing CRISPR to modify genetic sequences to enhance our wellbeing, to treat diseases, enhance the quality and quantity of food and handle ecological contamination. The molecular basis of physiological aging is sufficiently complex that we have not fully unraveled the processes and genes involved in it, even at this stage. However, we do have a few clues as what starts to break down over time and how and can therefore begin to think about how CRISPR could be employed to stop these processes. If we work systematically, CRISPR has the potential to help us solve the issue of disease occurrence, which could allow us to age without experiencing the current age-related decrease in quality of life. Diseases such as cancer, AIDS, blood disorder, cystic fibrosis, Huntington's disease and muscular dystrophy can be prevented or cured using CRISPR technology.

In cancer treatment, Hangzhou Cancer Hospital in China is currently testing the potential of the gene editing tool in patients with advanced cancer of the esophagus. Firstly, the patient's T cells are extracted. CRISPR is then used to remove the gene that encodes for a receptor called PD-1(program cell demise 1) that can bind to some tumors and prevents attack by the immune system. Lastly, the modified cells are transferredinto the patient with a higher capacity to attack tumor cells. At least 86 cancer patients have been treated with CRISPR in China [42].

CRISPR has been applied in the treatment of blood disorder. The first CRISPR trialin Europewas to treat beta-thalassemia, a blood disorder that affects the transport of oxygen in the blood [43]. A company known as CRISPR Therapeutics and Vertex Pharmaceuticalshas developed a therapy whichinvolvesusing CRISPR to make fetal hemoglobin from hematopoietic stem cells harvested from patience. The fetal hemoglobin is a natural form of the oxygen-carrying protein that binds oxygen much better than the adult form [44]. In 2018, United State carried out another preliminary treatment of sickle cell anemia, an inherited blood disorder caused by a transformation that deforms the red blood cells using CRISPR. The stem cells that generate red blood cells (hematopoietic blood cells), are taken from the patient and mutations are corrected by editing in the laboratory. The cells are then re-introduced into similar patients. The expectation is that by correcting the undifferentiated organisms, the cells they presently create will be ordinary, restoring the disease [45, 46].

AIDS could also be fought or treated using CRISPR bycutting off the HIV virus out of the DNA of immune cells [47]. This approach could attack the latent form of the virus which is inserted into our DNA, preventing most therapies from targeting it. The approach could also induce a natural resistance to HIV due to a mutation in a gene known as CCR5 (chemokine receptor type 5). CCR5encodes for a receptor on the surface of immune cells that HIV needs to get inside the cells. This prevents the virus from binding to the receptor due to the mutation in the gene structure. Early stage advancement of most CRISPR applications in HIV arebeing tested in animals before a clinical trial in humans can be planned.

Cystic fibrosis, a genetic disease that causes severe respiratory problems can be tackled using CRISPR technology. The life expectancy for a person with cystic fibrosis is only around 40 years after using the available treatments to deal with the symptoms. CRISPR technology could treat this disease from its origin by editing the mutations that cause it. This mutation is located in a gene called Cystic fibrosis transmembrane conductance regulator (CFTR). It has been demonstrated thatCRISPR could be used in human lung cells derived from patients with cystic fibrosis to fix the most common mutation behind the disease [48]. Editas Medicine and CRISPR Therapeutics are already testing its application in humans [49]. However, different CRISPR therapies need to be developed for different genetic defects since cystic fibrosis can be caused by multiple of different mutations in the CFTR gene. Editas has stated that it will focus at the most common mutations as well as some of the rare ones for which there is no treatment.

Another genetic disease known as muscular dystrophy that cause progressive weakness and loss of muscle mass can also treated using CRISPR technology. Duchenne's muscular dystrophy (DMD) is caused by mutations in the DMD gene, which encodes for a protein (dystrophin) necessary for the contraction of muscles [50]. Children born with this disease suffer progressive muscle dystrophy. Currently,there is no treatment available for DMD apart from palliative care. Research carried out in mice have shown that CRISPR could be used to fix the genetic mutations behind this disease [51]. Researchers in the US revealed a method that, instead of fixing each mutation individually, CRISPR was used to cut at 12 strategic mutation hotspots covering the majority of the estimated 3,000 different mutations that cause this muscular disease.Exonics Therapeutics Company is working on further development of this approach [51]. Also, another company known as Editas Medicine is following a broader approach which CRISPR removes whole sections of the protein containing mutations that make the protein shorter but remain functional [52].

Huntington's disease is caused by an abnormal repetition of a certain DNA sequence within the Huntington gene. The higher the abnormal repetition, the earlier the disease will manifest itself. It is tricky to treat Huntington's disease as any off-target effects poses more dangerous consequences in the brain than anywhere else in the body [52]. A version of CRISPR-Cas9 called KamiCas9 that includes a "self-destruct button" for the Cas9 enzymehave been developed by researchers in US [53]. CRISPR is used to cut the sequence of its own Cas9 enzyme. Also, a group of Polish researchers has opted for combining CRISPR-Cas9 with an enzyme called 'nickase' to make the gene editing more precise [54].

Apart from cellular senescence or aging, CRISPR can also be applied in the control of physical aging. It can be administered topically to reach a depth a few centimeters below the skin. Several companies are developing topical gels and creams to fight viral infections that live in reservoirs below the skin's surface. Therefore, using a CRISPR-based topical cream to boost collagen production or increase skin's elasticity and moisture may not be that far off. A research carried out at University of Alabama at Birmingham showed that aging-associated skin wrinkles and hair loss in a mouse model has been reversed.Anuclear gene mutation affecting mitochondrial functioncauses wrinkled skin and hair loss. Turning off the nuclear gene mutation restores the mouse to normal appearance [55]. The mutation is induced when the antibiotic doxycycline is added to the food or drinking water resulting in depletion of mitochondrial DNA due to the inactivation of the enzyme to replicate the DNA. A decline in mitochondrial function is seen during aging in humans and mitochondrial dysfunction can drive age-related diseasessuch as cardiovascular disease, diabetes, age-associated neurological disorders and cancer [56-58].

Telomere Engineering: Genetic manipulation of chromosomal telomeres has a great effect in the aging of cells. Shortening of telomeres due to lack of telomerase is linked with aging. Experimenton mice to examine what happens to mice once steps are taken to preventits telomeres from shortening was carried out by Ronald DePinho and a team of Harvard colleagues [59]. They bred a bunch of genetically modified mice that lacked the power to produce telomerase and watched as these mice showed speedyand extremely early onset symptoms of aging. These mice were later given injections

to re-activate the enzymetelomerase, expecting to be faced with the aging methodback to traditional levels. It was observed that the mice to aged backwards with their withered organs repairing themselves to the point of generation of new neurons in their brains. According to Cavallasca [60], experiments were conducted on mice by Spanish researchers in order to lengthen the mice health span and lifespan as they aged.The aim of the experiment was to treat 1 and 2 year old adult mice by injecting them with an adeno-associated virus (AAV) that can synthesize mice telomerase through the TERT (telomerase reverse transcriptase) protein. Their general health and lifespan were then compared to those of healthy mice of the same age. The mice under treatment showed better general and physical health compared to the control group and a longer lifespan (+24% in 1 year old mice, +13% in 2 years old mice). There was no higher tumor or cancer cells, despite the fact that an excess of telomerase can induce higher cell division and the creation of tumors and cancer cells [61].

On humans, there is great possibilities of treatment of ageing linked genetic diseasesbased on the scientific report from the Stanford University School of Medicine. They claim to have discovered a way to replenish the length of telomeres using a modified RNA (called modified TERT mRNA) containing the exact nucleotide sequence of telomerase reverse transcriptase (TERT) [62]. In their report, just three applications of this, within a few days, caused an increase in telomere length of as much as 10%, representing approximately 1,000 nucleotides. Cell division in human muscle cellswas increased approximately by three-fold with the use of this technology. It was an exciting discovery when the same routine was used with human skin cells. These cells divided around28 times more than the placebo. There have been successful experiments with TERT therapies but with issues of immune response to the modified enzyme in each case. There was no such response in the new technique employed by the team at Stanford. The rate at which division was increased suggests that any side effects could be limited for patients, due to the need for only short, infrequent applications.

Resetting Epigenetic Memory in Aged Stem Cells: The development of adult frogs from the transfer of tadpole intestinal somatic nuclei into oocytes showed that cellular memory of somatic cells can be reversed and even erased [63]. Evidence suggests that a similar approach might be applied to reset the molecular memory of aging cells. Somatic cell nuclear transfer of senescent fibroblasts from aged bovine donors results in cloned calves with fibroblasts that have restored population doubling and increased telomere maintenance compared to age-matched control animals [64]. It has been further proposed that reprogramming aged somatic cells into iPSCs (Induced pluripotent stem cells) or iPSC-like cells followed by redifferentiation to the desired somatic cell types may help reset the memory of aged somatic cells [65]. This possibility has been supported in part by studies in which aged hematopoietic progenitors were reprogrammed to produce iPSCs. These iPSCs were then used to create new HSCs (Hematopoietic Stem Cells) in a chimeric embryo system and yielded complete rejuvenation of hematopoietic activity.

CONCLUSION

Apart from rare mutations caused by viruses, radiation, unknown factors, individuals mostly have the same DNA from cradle to grave. Yet, humans and many other species that age in an accelerated or gradual manner obviously change during their lifespan. The Human genome project completed a decade back is a great breakthrough in science. Having the entire genome sequence of an individual from birth to old age would help to figure out all genome mutations caused by aging and alter them back using gene editing tools like CRISPR Cas9. Building predictive models from multiple individuals of different age using Machine learning (artificial intelligence) would facilitate the application of this gene editing technology without having to wait for an individual's genome data from birth to old age.

Although there are ethical issues to these advancement in genetic research, it has undoubtedly unraveledaging processes, how it affects our lives and how we can manipulate it to make our lives better. Even if death is not eradicated, people will be freed from the burden of age related diseases especially as a result of the recent application of gene therapy using the magnificent CRISPR technology. Challenge for future research would be to determine if these changes can be modeled fit for the entire populace in terms of cost, availability and ease of use.

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REFERENCES

1. Futurism., 2017. An End to Aging: Can Science Allow Humans to Become Immortal? https://futurism.com/1-evergreen-an-end-to-aging-heres-how-were-fighting-death
2. Gilbert, S.F., 2000. Aging: The Biology of Senescence. In *Developmental Biology* (6th ed). Sinauer Associates, Sunderland (MA).
3. Rodríguez-Rodero, S., J.L. Fernández-Morera, E. Menéndez-Torre., V. Calvanese, A.F. Fernández and M.F. Fraga, 2011. Aging Genetics and Aging. Aging Dis., 2(3): 186-195.
4. Lo, C.L., S.R. Choudhury, J. Irudayaraj and F.C. Zhou, 2017. Epigenetic Editing of Ascl1 Gene in Neural Stem Cells by Optogenetics. Scientific reports. 7: 42047.
5. Krokan, H.E and M. Bjørås., 2013. Base Excision Repair. Cold spring harbor perspective in biology. doi: 10.1101/cshperspect.a012583.
6. Qu, B., Y. Jia, Y. Liu, H. Wang, G. Ren and H. Wang, 2015. The detection and role of heat shock protein 70 in various non-disease conditions and disease conditions: a literature review. Cell Stress and Chaperones, 20(6): 885-92.
7. Mail Online. 2018. Could you live forever? Humans will achieve immortality using AI and genetic engineering by 2050, expert claims. https://www.dailymail.co.uk/sciencetech/article 5408425/Human-beings-achieve immortality-2050.html
8. Kuilman, T., C. Michaloglou, W.J. Mooi and D.S. Peeper, 2010. The essence of senescence. Genes Dev., 24: 2463-2479.
9. Salama, R., M. Sadaie, M. Hoare and M. Narita, 2014. Cellular senescence and its effector programs. Genes Dev., 28: 99-114.
10. Wu, X., H. Gao, W. Ke, M. Hager, S. Xiao, M.R. Freeman *et al*., 2011. Vent Xtrans-activates, pp: 53 and p16ink4a to regulate cellular senescence. J. Biol. Chem., 286(14): 12693-701.
11. Collado, M., M.A. Blasco and M. Serrano, 2007. Cellular senescence in cancer and aging, Cell, 30: 223-233.
12. Hanahan, D. and R.A. Weinberg, 2011. Hallmarks of cancer: the next generation, Cell, 144: 646-674.
13. Muñoz-Espín, D., M. Cañamero, A. Maraver, G. Gómez-López., J. Contreras, S. Murillo-Cuesta *et al*., 2013. Programmed cell senescence During Mammalian Embryonic Development. Cell, 155: 1104-1118.
14. Storer, M., A. Mas., A. Robert-Moreno, M. Pecoraro, M.C. Ortells, V. Di Giacomo, *et al*., 2013. Senescence is a developmental mechanism that contributes to Embryonic Growth and Patterning. Cell, 155: 1119-1130.
15. Niccoli, T. and L. Partridge, 2012. Ageing as a risk factor for disease. Curr. Biol., 22: 741-752.
16. De-Magalhães, J.P., 2013. How ageing processes influence cancer. Nat. Rev. Cancer., 13: 357-365.
17. North, B.J. and D.A. Sinclair, 2012. The intersection between aging and cardiovascular disease. Circ. Res., 110: 1097-1108.
18. Querfurth, H.W. and F.M. LaFerla, 2010. Alzheimer's disease. N. Engl. J. Med., 362: 329-344.
19. López-Otín, C.M., A. Blasco, L. Partridge, M. Serrano and G. Kroemer, 2013. The hallmarks of aging. Cell, 153: 1194-1217.
20. McCabe, P., 2017. Senescence in Plants. https:// doi.org/ 10.1002/ 9780470015902.a0020133.pub2
21. Ritchie, H. and M. Roser, 2018. Causes of Death". Published online at Our World In Data.org. Retrieved from: 'https://ourworldindata.org/causes-of-death' [Online Resource]
22. Reape, T.J., E.M. Molony and P.F.J. McCabe, 2008. Programmed cell death in plants: distinguishing Between Different Modes, 59(3): 435-44.
23. Zimmerman, L., 2010. Must all organisms age and die? Massachusetts Institute of Technology, School of Engineering. http:// engineering.mit.edu/ live/news/1223-must-all organisms age-and-die.
24. Villazon, L., 2018. How long does a bacterium live? Science Focus. https://www.sciencefocus.com.
25. Guerin, J., 2004. Emerging area of aging research: long-lived animals with "negligible senescence, Annals of the New York Academy of Sciences, 1019(1): 518-520.
26. Rose, M.R., 1991. Evolutionary Biology of Aging. New York: Oxford University Press.
27. Hayflick, L. and P.S. Moorhead, 1961. The serial cultivation of human diploid cell strains. Exp. Cell Res., 25: 585-621.
28. Kotz, D., 2010. Fight These 4 Causes of Aging. https:// health.usnews.com/ health-news/ familyhealth/ living-well/ articles/2010/07/29/fight-these-4-causes-of-aging
29. Bai, P. and C. Cantó, 2012. The Role of PARP-1 and PARP-2 Enzymes in Metabolic Regulationand Disease, Cell Metabolism, 16(3): 290-95.

30. Cavallasca, J., 2017. Aging 101: Biological causes of aging. http:// www.longlonglife.org/ en/ transhumanism-longevity/ aging/biological-causes-aging/
31. Campisi, U., 2005. Senescent Cells, Tumor Suppression and Organismal Aging: Good Citizens, Bad Neighbors, Cell, 120(4): 513-22.
32. Lin, Y.J., L. Seroude and S. Benzer, 1998. Extended life-span and stress resistance in the Drosophila mutant methuselah. Science, 282: 943-946.
33. Mesquita, A., M. Weinberger, A. Silva, B. Sampaio-Marques, B. Almeida, C. Leão *et al*., 2010. Caloric restriction or catalase inactivation extends yeast chronological lifespan by inducing H_2O_2 and superoxide dismutase activity. Proceedings of the National Academy of Sciences of the United States of America, 107(34): 15123-15128.
34. Kaushik, S. and A.M. Cuervo, 2015. Proteostasis and Aging. Nature Medicine, 21(12): 1406-1415.
35. Beerman, I., C. Bock, B.S. Garrison, Z.T. Smith, H. Gu, A. Meissner, *et al*., 2013. ProliferationDependent Alterations of the DNA Methylation Landscape Underlie Hematopoietic Stem Cell Aging. Cell Stem. Cell, 12(4): 413-425.
36. Rübe, C.E., A. Fricke, T.A. Widmann, T. Fürst, H. Madry, M. Pfreundschuh *et al*. 2011. Accumulation of DNA damage in hematopoietic stem and progenitor cells during human aging. PLoS ONE. 6 (3): e17487. https:// doi.org/ 10.1371/ journal.pone.0017487
37. Kuro-o, M., Y. Matsumura, H. Aizawa, H. Kawaguchi, T. Suga, T. Utsugi *et al*., 1997. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature, 390: 45-51.
38. Michikawa, Y., F. Mazzucchelli, N. Bresolin, G. Scarlato and G. Attardi, 1999. Aging-dependent large accumulation of point mutations in the human mtDNA control region for replication. Science, 286: 774-779.
39. Saltus, R., 2010. Partial reversal of aging achieved in mice. https:// news.harvard.edu/ gazette/ story/ 2010/ 11/ partial-reversal-of-aging-achieved-in mice/
40. Vidyasagar, A., 2018. What is CRISPR. Available at http:// www.Livescience.com/crispr. Accessed on 12th September, 2018.
41. Nishimasu, H., F.A. Ran., P.D. Hsu, S. Konermann, S.I. Shehata, N. Dohmae, *et al*., 2014. Crystal structure of Cas9 in complex with guide RNA and target DNA. Cell, 156(5): 935-949.
42. Normile, D., 2017. China sprints ahead in CRISPR therapy race. Science, 358(6359): 20-21.
43. Terry, M., 2018. CRISPR Therapeutics Plans to Treat First Patients for Beta Thalassemia in Europe. https://www.biospace.com/
44. Iamius, 2018. 9 Incurable Diseases That Can Be Cured - By Using CRISPR Gene Editing Tool. https:// explorebiotech.com/
45. Cross R., 2016. CRISPR edits sickle cell mutation. Chemical & Engineering News, 94(41): 5 News of the week.
46. Pharmaphorum, 2018. FDA gives go-ahead for CRISPR-based sickle cell disease trial. https:// pharmaphorum.com/ news/fda-gives-go-ahead-for-crispr-based-sickle-cell-disease trial
47. Ebina, H., N. Misawa, Y. Kanemura and Y. Koyanagi, 2013. Harnessing the CRISPR/Cas9 system to disrupt latent HIV-1 provirus. Sci Rep., 3: 2510.
48. Marangi, M. and G. Pistritto, 2018. Innovative Therapeutic Strategies for Cystic Fibrosis: MovingForward to CRISPR Technique. Front in Pharmacol., 9: 396.
49. Shaffer, C., 2018. Could CRISPR Repair CFTR in Cystic Fibrosis Patients? https://www.news medical.net/health/Could-CRISPR-Repair-CFTR-in-Cystic-Fibrosis-Patients.aspx
50. Martel, J., 2017. Muscular Dystrophy: Types, Symptoms and Treatments. https:// www.healthline.com/ health/muscular-dystrophy
51. UT Southwestern Medical Center., 2018. New CRISPR method efficiently corrects Duchenne muscular dystrophy defect in heart tissue. Science Daily. www.sciencedaily.com/ releases/ 2018/ 02/ 180206121017.htm
52. Fernandez, C.R., 2018. 7 Diseases CRISPR Technology Could Cure.https:// labiotech.eu/ tops/ crispr-technology-cure-disease/
53. Eisenstein, M., 2018. CRISPR takes on Huntington's disease. Nature, 557: 42-43.
54. Dabrowska, M., W. Juzwa, W.J. Krzyzosiak and M. Olejniczak, 2018. Precise Excision of the CAG Tract from the Huntingtin Gene by Cas9 Nickases. Front. Neurosci., 12: 75.
55. Singh, R., T.R. Schoeb, P. Bajpai, A. Slominski and K.K. Singh, 2018. Reversing wrinkled skin and hair loss in mice by restoring mitochondrial function, Cell Death & Disease, 9: 735-748.
56. Gunasekaran, U. and M. Gannon, 2011. Type 2 diabetes and the aging pancreatic beta cell, Aging., 3: 565-575.

57. Kwon, Y.H., J.H. Fingert, M.H. Kuehn and W.L. Alward, 2009. Primary open-angle glaucoma. N. Engl. J. Med., 360: 1113-1124.
58. Sun, N., R.J. Youle and T. Finkel, 2016. The Mitochondrial Basis of Aging. Mol. Cell, 61(5): 654-666.
59. Landau, M., 2013. An Interview with Ronald DePinho. Clinical Chemistry, 59(1): 11-17.
60. Cavallasca, J., 2018. Part 5: Fight aging with telomere therapy.http://www.longlonglife.org/en/transhumanism-longevity/aging/telomeres-andaging/fight-aging-telomere-therapy/
61. Bernardes de Jesus, B., E. Vera, K. Schneeberger, M.A. Tejera., E. Ayuso, F. Bosch *et al*., 2012. Telomerase gene therapy in adult and old mice delays aging and increases longevitywithout increasing cancer. EMBO Molecular Medicine, 4(8): 691-704.
62. Blau, H., 2015. Telomere extension turns back aging clock in cultured human cells, study finds.https://med.stanford.edu/ news/all-news/2015/01/telomere-extension-turns-back-agingclock-in-cultured-cells.html
63. Tokmakov, A.A., T. Iwasaki, K. Sato and S. kamada, 2016. Reprogramming of somatic cells and nuclei by *Xenopus*oocyte and egg extracts, Int. J. Dev. Biol., 60: 289-296.
64. Xu, J. and X. Yang, 2001. Telomerase Activity in Early Bovine Embryos Derived from Partheno genetic Activation and Nuclear Transfer. Biology of Reproduction, 64(3): 770-774.
65. Singh, V.K., M. Kalsan, N. Kumar, A. Saini and R. Chandra, 2015. Induced pluripotent stem cells: applications in regenerative medicine, disease modeling and drug discovery, Front Cell Dev. Biol., 3: 2.