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The Molecular and Medical Aspects of the Aging Process

[1]S. Mulambalah Chrispinus, [1]N. Siamba Donald and [2]M. Vulule John
[1]Department of Biological Sciences, Masinde Muliro University of Science and Technology, P.O. Box 190 Postcode 50100, Kakamega, Kenya
[2]Kenya Medical Research Institute, P.O. Box 1578 Postcode 40100, Kisumu, Kenya

Abstract: The human body undergo many physiological, chemical changes from birth and year after year as growth and development occurs. Many of these changes are clearly documented and others are not and are unknown. It is true that not all is completely known of the changes that are accumulating in the bodies with the passing of time. The mind and body gradually degrade with age, losing their former vigour and resulting in a wide range of effects. Memory is weakened, motor skills decline, bones become brittle and skin loses elasticity which is attributed in part to molecular changes. Aging is also marked by an increased susceptibility to infection and disease partly because of the decline of the immune system in its effectiveness in fighting pathogens and abnormal cell growth. Every year, countless attempts are made to reverse aging and recapture youth. A great amount of money is spent on cosmetic procedures and chemical substances such as creams and lotions in attempts to restore youthful appearances. The number of surgeries in senior citizens world-wide has greatly increased over the recent past with more people over the age of 50 seeking operations to prolong and improve their lives. While the search for the elusive fountain of youth is no new phenomenon, recent research has yielded findings that could shed more light on the molecular and medical aspects of the aging process. The study reviews the research findings on the molecular and medical aspects associated with aging in humans and attempts made to slow and or reverse the aging process.

Key words: Human body, chemical changes, growth, new phenomenon, medical aspects

INTRODUCTION

The evolution aging process and associated conditions: It is difficult to give a good definition of aging that holds for all organisms but for populations a very useful description is that aging consists of all those processes that lead to a monotonic increase of mortality with time. Humans for instance have a low mortality of roughly 0.1% at age 20 but of about 10% at 80 years of age. Aging is a complex biological process that affects practically all components of the human body. There are two different aspects of the aging process that need to be understood.

First, there is the question of why the aging process has evolved. A process that leads to an increase of mortality reduces the average life span of the organism and thus reduces the number of offspring the organism can have. This however should lead directly to a reduction of evolutionary fitness. It is therefore, not trivial to understand why such a biological trait should have evolved in practically all higher organisms.

The second important question is of course how the actual biochemical mechanism works leading to the gradual functional decline. Unfortunately, the evolutionary models do not predict specific mechanisms that might be involved in aging. As a consequence a large number of mechanistic models have been proposed. A review of the available literature suggests that >300 different mechanistic theories exist (Medvedev, 1990). The most popular mechanistic theories reflect overlap and points of interaction between the different theories. For example, oxygen radicals can damage DNA, leading to somatic mutations or damage mitochondrial membranes and DNA, leading to defective mitochondria. Radical reactions with cytoplasmic or mitochondrial proteins or membranes can also lead to the accumulation of indestructible waste products and finally, reactions of radicals with macromolecules can lead to the formation of cross-links that impair their biological functioning that ultimately result in aging.

Man may not be aware of the changes that accumulate in the body with passing time. The mind and the body gradually degrade with age, losing former vigour and result in a wide range effects. The memory becomes weakened, motor skills decline, bones become brittle and

Corresponding Author: S. Mulambalah Chrispinus, Department of Biological Sciences, Masinde Muliro University of Science and Technology, P.O. Box 190 Postcode 50100, Kakamega, Kenya

skin loses elasticity. Aging is also marked by increased susceptibility to infection and disease partly due to decline in the immune system effectiveness (Gardner, 1980).

World-wide, attempts are made to reverse the human aging process. Chemical substances for instance creams, lotions are widely used to either maintain or restore youthful appearances. The numbers of surgeries in senior citizens has increased of people seeking operations to prolong and improve their lives. Recent research finding on a Telomere Activator extract (TA-65) from a medical plant has raised both excitement and controversy on the possibility of rewinding the aging process and prolong human lifespan (Jesus *et al*., 2011).

Theories of evolution of aging: The first attempt to explain the evolution of aging was made by Weismann (1891). He proposed that aging is beneficial by removing crippled and worn-out individuals from the population and thus making space and resources available for the next generation. This type of reasoning is very similar to suggestions such as the prevention of overcrowding or the acceleration of evolution by decreasing the generation time.

These ideas suggest that aging itself confers a selective advantage and that the evolution of genes that bring life to an end is an adaptive response to selective forces. All these theories have in common that they rely on group selection, the selection of a trait that is beneficial for the group but detrimental to the individual. However, group selection works only under very special circumstances such as small patch size and low migration rates (Smith, 1976). A second major argument against adaptive theories is the empirically found paucity of old individuals in natural populations. Extrinsic mortality in natural populations is so high that only very few individuals survive long enough to be killed by intrinsic mortality. But if intrinsic mortality which is caused by the aging process is not the main cause of death under natural conditions, it is difficult to see how aging could have evolved for the purpose of removing animals from the population.

The weaknesses of adaptive theories have been recognized for some time and newer theories are no longer based on group selection but rather on the declining force of natural selection with time. This important concept is based on the fact that even in the absence of aging individuals in a population are always at risk of death due to accidents, predators and diseases. For a given cohort this leads to an exponential decline over time in the fraction of individuals that are still alive. Events for instance biochemical processes that occur only in chronologically old individuals will therefore affect only a small proportion of the whole population. The later the onset of the events, the smaller the involved fraction of the population is Medawar was the first to present a theory for the evolution of the aging process based on this idea. His Mutation-Accumulation Theory states that aging might be caused by an accumulation of deleterious genes that are expressed only late in life. Because of the declining force of natural selection, only a small part of the population would be affected by this type of mutation and the resulting selection pressure to remove them would only be very weak. Mutations with a small selection pressure to be removed can persist in a mutation-selection balance and thus explain the emergence of an aging phenotype.

Another theory of this kind is the Antagonistic Pleiotropy Theory (Williams, 1957). Genes that affect two or more traits are called pleiotropic genes and effects that increase fitness through one trait at the expense of a reduced fitness of another trait are antagonistic. Now consider a gene that improves the reproductive success of younger organisms at the expense of the survival of older individuals. Because of the declining force of natural selection such a gene will be favored by selection and aging will occur as a side effect of the antagonistic pleiotropy property of this gene. Possible candidate genes might be found in human males and females. Prostate cancer appears frequently in males at advanced ages but it can be prevented by administration of female hormones or castration. It seems to be a consequence of long-term exposure to testosterone which is necessary for male sexual and thus reproductive, success. In older females osteoporosis is mediated by estrogens that are essential for reproduction in younger women. In both cases, gene effects that are beneficial at younger ages have negative consequences later in life.

Genes that trade long term survival against short-term benefit are probably the strongest candidates to explain the aging process. A specific version of this hypothesis that connects evolutionary concepts with molecular mechanisms is the disposable Soma Theory (Kirkwood and Holliday, 1986; Kirkwood and Rose, 1991). The theory realizes that organisms have a finite energy budget that must be distributed among different tasks like growth, maintenance and reproduction. Energy spent for one task is not available for another. Organisms have to solve this optimal resource allocation problem such that evolutionary fitness is maximized (Stearns, 1992). The rationale for this postulation is the idea that aging is caused by the accumulation of some kind of damage and that by investing more in repair, the accumulation rate is slowed down until finally the incidence rate is equal to the

removal rate in which case the physiological steady state can be maintained indefinitely. This fits quite nicely with biological data. Species like mice or rabbits live in a high-risk environment and as predicted, they invest heavily in offspring but have little left for maintenance. Consequently, their aging rate is high and their life expectancy is low (even under risk-free laboratory conditions). Humans by contrast inhabit a low-risk environment, expend fewer resources for offspring and invest more in repair. Especially instructive are birds which live 2-3 times as long as mammals of comparable body weight. Again this long life span can be predicted by the enormous reduction of external mortality that accompanies the ability to fly and thus escape predators or starvation.

Another important aspect of aging is that the optimal level of maintenance and repair of tissue damage is always below the critical level. This result can also be understood intuitively. Since, all species have an external mortality that is above zero, they have a finite life expectancy even without aging. This means that even though it might be physiologically possible to have such an efficient repair system that damage does not accumulate with time resulting in a potentially immortal organism this never results in a maximal fitness value.

Although, the Disposable Soma Theory is very successful in explaining the evolution of the aging process, it unfortunately does not predict which specific molecular damage accumulates or which repair systems are the most important. All possible mechanisms that somehow influence the steady state of the cell are viable candidates. Indeed this can be taken as an argument that many types of damage accumulate with time and that many types of repair processes contribute to the rate of aging. Under those conditions it is not fruitful to study individual biochemical mechanisms in isolation but rather as a network of connected processes. The investigation of the aging process is thus a prime candidate for a systems biological approach and molecular biology.

MOLECULAR BASIS OF AGING

Accumulation of defective mitochondria: Defective mitochondria play a prominent role in one of the most favored theory regarding the biochemical mechanism of the aging process. Mitochondria are not only the powerhouses of the cell, generating the majority of the cellular ATP but also are the main producers of Reactive Oxygen Species (ROS). These reactive molecules damage proteins, membranes and the mitochondrial DNA (mtDNA). The Mitochondrial Theory of Aging is based on the fact that damage to the mtDNA impairs the genes responsible for ATP production but not those involved in the replication of the mtDNA because they are located in the nucleus. Thus ROS-induced damage to the mitochondria could lead to a progressive decline in the cellular energy supply. Experimental findings have confirmed that in aging post-mitotic cells there is a clonal accumulation of defective mitochondria with time (Brierley *et al*., 1998). The actual molecular mechanism of this accumulation remains unclear because of the difficulty in distinguishing mutant mitochondria from the normal type. A possible explanation rests on the fact that mitochondria, like proteins have a certain turnover rate. Newly synthesized mitochondria typically exist within the cell only for a short period after which they are degraded (Huemer *et al*., 1971; Menzies and Gold, 1971). Mitochondrial mutants can therefore accumulate in a population either by increasing their division rate or by lowering their rate of degradation. Therefore, it has been suggested that damaged mitochondria accumulate because they have a slower degradation rate (De Grey, 1997). If it is furthermore reported that defective organelles actually grow more slowly than normal type (Kowald and Kirkwood, 2000). This explains clonal expansion and avoids the energy paradox that arises if defective mitochondria are required to have a faster proliferation rate. The idea is that individual mitochondria are targeted for turnover in accordance with the level of oxidative damage to their inner mitochondrial membrane.

The more the membrane is damaged, the sooner the mitochondrion is destroyed. Defective mitochondria have decreased respiratory activity and it is therefore assumed that they inflict less oxidative damage to their membranes than do wild-type mitochondria. Furthermore, mitochondria also accumulate damage to their membranes, defective organelles that have acquired some form of mtDNA damage have a mitochondrial turnover is proportional to the level of membrane damage. Once mitochondria have suffered DNA damage, further reactions with radicals increase the amount of membrane damage. The presence of antioxidants counteract the damaging effect of radicals (provide a sink for radicals) and their absence would otherwise enhance cell damage. The different classes of mitochondria produce different amounts of ROS which cause the transition of mitochondria from one damage class to another. Finally, the mitochondria are degraded with a rate constant that is proportional to the amount of membrane damage.

Mitochondria synthesis rates: Mitochondria are continually being turned over which means that new mitochondria must be synthesized to balance degradation. It is assumed that the synthesis rate is controlled by the

cellular energy level. A low ATP concentration stimulates mitochondrial growth while a high concentration diminishes it. This is known as product inhibition. Although, mitochondria contain their own genetic material, they cannot be treated as self-replicating entities because the genes coding for the overwhelming majority of their proteins are located in the nucleus and these proteins have to be imported from the cytoplasm.

However because of the assumed growth disadvantage of defective mitochondria, the contributions to the different classes have to be weighted. All mitochondria with DNA damage have the same Growth Disadvantage (GD) because their oxidative phosphorylation is non-functional. GD is the factor by which the growth rate is reduced compared to intact mitochondria. The same growth disadvantage is assumed for mitochondria with intact DNA but with the highest amount of membrane damage. For mitochondria with intact DNA and a medium amount of damage, there is a growth disadvantage whereby the overall growth rate is reduced by half. This has a bearing on the cell division and the aging process.

Radical levels: The rate of synthesis/generation and accumulation of numbers of radicals in a cell will have different effects on the mitochondria. Intact mitochondria suffer minimal effect from the presence of radical. However, damaged mitochondrion and its mtDNA will suffer most from presence of radicals. It is assumed that radicals are generated at a fixed rate and that their removal is proportional to the existing amount of radicals in the mitochondria. However, the rate of radical production of intact mitochondria is lower and the production rate of radicals in defective mitochondria is increased. This explains the high accumulations of radicals in defective mitochondria a phenomenon associated with the aging process.

Dilution of membrane damage: A fast mitochondrial growth acts as a rejuvenation mechanism because it dilutes membrane damage. When newly synthesized components are incorporated into the mitochondrial membrane, the pre-existing level of membrane damage is reduced and the New Damage Level (NDL) is the result of mixing existing membrane components with the new ones. If for example, the amount of new membrane components is equal to the existing ones, NDL is 50%. This suggests that for all mitochondria with a growth disadvantage of GDF, synthesis and degradation will be high. However, synthesis is controlled by the ATP level and the antioxidant promoter. As for mitochondria with damaged membranes, it is possible that a low level of ATP will be experienced which also diminishes the protein synthesis rate, a situation common in aging cells and organisms. The generation of energy is directly proportional to the proposed growth disadvantage, therefore growth diminishes with age a phenomenon closely associated with aging in humans. It is therefore, essential to investigate the consequences of cell division on the stability of the mitochondrial population to understand the aging process (Kowald and Kirkwood, 1999, 2000).

AGING AND ANTI-AGING RESEARCH EXCITEMENT AND CONTROVERSY

Aging linked to telomeres: Aging is linked to the shortening of telomeres (Bhamidi, 2011; Jesus *et al*., 2011) which are repeated DNA sequences found at the end of chromosomes. Characterized by TTAGGG repeats and protected by a protein complex called shelterin, mammalian telomeric DNA ensures the stability and proper replication of DNA, thereby maintaining cellular health (De Lange, 2005; Harley *et al*., 1990). Because they function as the protective tips of chromosomes, telomeres prevent degradation of the chromosome by undergoing degradation themselves during DNA replication and cell division (Hayflick and Moorhead, 1961; Harley *et al*., 1990). In 1961, it was discovered that this degradation of telomeric DNA causes a stage at which the cell can no longer divide (Hayflick and Moorhead, 1961). In other words as the cell divides, telomeres shorten until they become too short. At this point, cells achieve replicative senescence and are unable to divide further, thereby leading to the various changes that are associated with aging (Telomerase Activation Sciences).

Studies illustrate the association between telomere shortening and the various changes related to advancing age. Researchers have used fibroblast cells as a tool to explore this relationship. Fibroblasts are ideal for aging studies since, they are characterized by four stages of development and have finite replicative capacity. In the first two stages, growth, development and proliferation of cells occur. In the third stage, the ability of the cells to replicate declines and many cells begin to undergo death or apoptosis. By the fourth stage, the cells, now resembling aged cells have completely lost their ability to replicate and do not even respond to growth factors (Cristofalo and Pignolo, 1993). A study conducted on human fibroblasts from donors of varying ages, demonstrate a relationship between age and telomere length. Southern blotting analysis was used to measure the length of telomeric DNA in fibroblasts obtained from donors of various ages. A statistically significant inverse relationship was observed between the donor age and

telomere length: as age increased, the length of telomeric DNA decreased (Harley *et al*., 1990). It is therefore evident that telomere shortening appears to occur in an age-dependent fashion.

Degradation of telomeric DNA is not only linked to aging but also plays a role in a myriad of diseases. Telomere degradation can result from some genetic diseases such as Down's Syndrome and Aplastic anaemia or from genetic mutations affecting telomere structure and replication. Chronic stress and infections can also lead to telomere shortening which then causes premature aging syndromes and other age-associated diseases (Harley, 2005). For example, studies have found that people with shorter than average telomeres are more susceptible to heart disease and stroke this corresponds with past findings that older people who have shorter telomeres than their younger counterparts are more likely to develop these conditions (Von Zglinicki *et al*., 2000). Dyskeratosis congenita is a disease characterized by shortened telomeres due to mutation (Cawthon *et al*., 2003). Individuals with this condition are born with degraded telomeric DNA which causes abnormal nail formation, pigmentation of the skin and sores within the mouth (Savage and Alter, 2009). By stopping cell division, telomere shortening can cause damage of proliferative tissue or tissue that typically may have high levels of cell division. For example, telomere shortening can prevent renewal of tissue in the lungs causing an increased risk of pulmonary fibrosis or scarring of fibrous connective tissue in the lungs, leading to problems commonly experienced with aging. Shortening of telomeres leads to a wide range of negative effects therefore, it has been proposed that pharmacological elongation of telomeric DNA would be able to counter these issues (Harley, 2005).

The role of enzyme telomerase: Telomere terminal transferase-more commonly known as telomerase is an enzyme that elongates telomeric DNA by attaching TTAGGG sequences to the ends of chromosomes (Shay/Wright Laboratory). Consisting of protein and RNA subunits, telomerase is capable of replacing telomeric DNA that has been lost due to cell replication. This enzyme is found in high levels in fetal and embryonic cells because these cells are growing and developing and since, cell division is extremely important at this stage. On the other hand, the extremely low levels of telomerase in cells of the adult body lead to telomere shortening causing aging to occur (Wright, 1996; Ulaner and Giudice, 1997). Experiments performed with human cells in culture have revealed that while normal cells that have not been treated with telomerase undergo shortening of their telomeres and thereby age, cells that have been treated with this enzyme function more effectively and retain the ability to divide for a longer period of time (Harley, 2005). Furthermore even under stress, cells in the presence of telomerase do not lose their ability to divide and grow. Ultimately, cells treated with this enzyme retain the characteristics of young and healthy cells.

While administering telomerase to human cells may reverse aging and treat degenerative diseases by allowing replenishment of cells and proliferative tissues this pharmacological intervention also poses the threat of causing cancer. Degradation of telomeres causes apoptosis of cells that proliferate excessively, thereby preventing formation of tumors (Folini *et al*., 2011; Harley, 2005). Therefore, even if cells are able to divide excessively, they will still be induced to undergo apoptosis, thereby averting formation of a tumor. However, the presence of telomerase tampers with this mechanism by preventing the degradation of telomeric DNA and allowing somatic cells to break the cycle of aging and become immortal. Telomerase-induced elongation of DNA has been shown to occur in most human cancers probably since high or unregulated levels of telomerase allow cells to divide without limit (Harley *et al*., 1990). For example, high levels of telomerase were found in HeLa cells cultured for research (Liu *et al*., 2011). Therefore, rendering human somatic cells immortal may cause them to become cancerous.

Telomerase activator in the anti-aging process: Telomerase activator known as TA-65 elongates telomeric DNA without increasing cancer risk. In a recent study (Jesus *et al*., 2011), TA-65 obtained from a traditional Chinese medicinal plant known by its scientific name as *Astragalus membranaceous* was found to activate activating *Terc* gene in mice required to manufacture telomerase. TA-65 activated telomerase production resulting in elongation of very short telomeres and reversal of DNA damage. In addition to this, adult mice this molecule also increased overall glucose tolerance, improved skin health of female and decreased osteoporosis risk all associated with aging. Even though the mice that were given TA-65 had an increased incidence of liver cancer in comparison to the mice in the control group this difference was statistically insignificant and therefore dismissed (Jesus *et al*., 2011). Thus, it suggested that TA-65 is able to elongate telomere length and allow tissue replenishment without increasing cancer risk.

Based on the telomere-elongating capabilities of TA-65 molecule, a nutraceutical capsule named TA-65 that delivers the anti-aging benefits of this telomerase

activator in humans has been developed (Telomerase Activation Sciences, TAS). Physicians are collaborating with the company (TAS) and have carried out clinical trials. People who enrol on this protocol will consume prescribed capsules per day; expected results are longer telomeres, a stronger immune system increased bone density and a decline in other age-related degenerative effects. Possible effects that are not guaranteed by T.A Sciences include increased energy increased endurance, sexual enhancement and a general sense of well being (Telomerase Activation Sciences).

The manufacture and marketing of a pill that claims to reverse aging has raised a great amount of controversy and excitement. Concerns have been voiced on the issue that there is no overall elongation of all telomeres in studies concerning TA-65. While extremely short telomeres elongate in response to the activator, the same cannot be said about the others since an increase in telomeres of average length does not take place. Therefore, the TA-65 supplement may not function in exact accordance as reported. Woynarowski (2011) pointed out that the study on TA-65 was done with mice as subjects. The mechanism of aging in mice is different from that in humans; aging in mice is more complex and does not consist of only telomere shortening.

Other professionals in the field of age research bring up another potential issue associated with TA-65: the use of telomerase. Research on aging has brought up the topic of cancer and its link to telomerase. It cannot be overlooked that the mice given TA-65 did develop liver cancer even though the incidences did not reach statistical significance. There are concerns that telomere elongation could possibly extend the life of cancerous cells that would typically die in the absence of TA-65 hence, its use in humans could lead to increased incidence of cancer. However, it is argued that telomerase activation by TA-65 could maintain immune cells and allow them to fight cancerous cells.

It is believed that the positive outcomes promised by the pill (TA-65) far outweigh the negative effects that it might result. However, research has found that making a comprehensive lifestyle change in terms of diet, exercise and stress reduction habits leads to increased telomerase activity in a more natural manner and thereby produces similar results (Ornish *et al*., 2008). In a study conducted and involving group of 30 men with low-risk prostate cancer were enrolled in a comprehensive lifestyle modification program. For 3 months, they consumed a low fat diet rich in fruits, vegetables, unrefined grains and legumes, participated in moderate aerobic exercise and practiced relaxation techniques such as yoga, stretching and meditation. At the end of the program, their telomerase activity was measured. The results of this comprehensive lifestyle change included a significant increase in telomerase activity, a drop in Low Density Lipoprotein (LDL) cholesterol levels and a decrease in psychological distress (Ornish *et al*., 2008). As a result of this program, the subjects of the study emerged as healthier, more relaxed individuals. Therefore, TA-65 is not the only method of increasing telomerase activity and improving overall health; natural lifestyle modifications have a similar effect and are significantly less expensive with no known adverse reports.

CONCLUSION

In this study, organism is generally characterized by the declining ability to respond to stress increasing homeostatic imbalance and increased risk of disease. Because of this, death is the ultimate consequence of aging. Differences in maximum life span between species correspond to different rates of aging. For example inherited differences in the rate of aging make a mouse elderly at 3 years and a human elderly at 90 years. These genetic differences affect a variety of physiological processes, probably including the efficiency of DNA repair, antioxidant enzymes and rates of free radical production. Despite the controversy surrounding TA-65, it must be acknowledged that its discovery denotes a great stride in the field of aging research. Future research and clinical trials concerning this anti-aging compound have the ability to elucidate its properties and implementations. Therefore, TA-65 promises to be of great use as a base for future research on aging and ant-aging.

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