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Senescence of Cell

Samah Ibrahem Ahmed [1]

[1] samahubady@gmail.com

Annotation: Cellular senescence is the cessation of cell division in multicellular organisms' somatic cells. It causes the depletion of energy reserves necessary for cell division. The inability to proliferate prevents senescent cells from synthesizing new DNA and sustaining growth (Cotter MA et al., 2007; Smith OM, 1996; Smith JR, Pereira-).

Introduction

Hayflick and Moorhead (1961) coined the term "replicative senescence" because, after a limited number of divisions in the culture medium, human diploid fibroblast cells stopped replicating and developing (Ben-Porath I, Weinberg RA, 2004).

Normal primary cells derived from living organisms divide swiftly at first in a culture medium, but their division rate ultimately slows and stops. The predetermined number of cell divisions in the pre-senescence stage is commonly referred to as the "Hayflick limit," which is approximately 50. These divisions lead to replicative or duplicate senescence (De Magalhaes JP, 2004).

Mooiweer et al., 1994; Sandhu AK et al., 2006) and Mooiweer et al., 2006) have identified alterations in the external appearance of aged cells, including surface irregularities, increased size, and loss of invaginations. Among the distinguishing characteristics of senescent cells are gene expression alterations. In addition, reproductive factors, enzymatic susceptibility, and immunogenic protein mediators (cytokines) vary (Itahana et al., 2004).Senescent cells can also be identified by the presence of specific biological markers, such as beta-galactosidase, an enzyme that degrades lactose and is not present in normal cells but is associated with replicative senescence (Braig M et al., 2005; Chen JH et al., 2007).

Senescence has been observed in numerous other cell types, including epithelial cells, keratinocytes, T lymphocytes, and dendritic cells, in addition to human diploid fibroblast cells. In the culture medium, these cell types endure a limited number of divisions and then discontinue dividing. Researchers (Berabe NG et al., 1998) reported that cell senescence is associated with the aging process in various organisms, attributing this association to mechanisms believed to result in the irreversible loss of replicative capacity in cellular populations. Extensive research has been conducted in recent decades on the aging process, using cell culture outside the living organism and observing the ongoing cellular changes within and outside the body as organisms age.

In this regard, human diploid fibroblasts have been utilized as dual-stained stem cells (chromosomes) (Siitonen et al., 2004; Campisi J., 2001; De Magalhaes JP). Gene expression and cellular performance or behavior are affected by genetic and epigenetic (transient) variations (Spencer CC et al., 2003; Hardy K et al., 2005).

The research query is whether the observable loss of cellular division mechanism in cultured cells precisely parallels the aging-related mechanism in living organisms. It has been observed that all animal somatic cells undergo cellular senescence, with the exception of primordial cells and cancer

cells, which do not undergo cellular senescence and are therefore referred to as immortal or enduring cells. (Wright wf. and Shay JW., 2001; patilck et al., 2005).

Genetic and hereditary pathways are implicated in the aging process of living organisms, as shown by research conducted on senescent cells both inside and outside the body (Berabe NG et al., 1998). In these organisms, they have also confirmed a connection between cellular senescence, aging, and malignant tumors. Except for a few rare cases, all living organisms undergo senescence as they age, with the exception of a few rare cases that do not undergo cellular senescence. One example of such organisms is "Hydra," a member of the phylum Cnidaria, which lacks signs of cellular senescence and demonstrates a high degree of tissue renewal and regeneration, a low mortality rate, and other characteristics indicating potential longevity or sustained survival (Martinez DE, 1998; Campisi J. 2005).

The extended lifespan or longevity of Hydra and its ability to bypass cellular senescence at the cellular level may indicate that cellular renewal capacity does not decline. Age-related characteristics include the irreversible cessation of cell division. It is essential to emphasize that the senescence phase is distinct from the typically observed quiescent or inert phase in cells.

Quiescence, also known as the quiescent state, is a reversible process involving the cell's ability to re-enter the cell cycle. In contrast, senescence is characterized by a loss of responsiveness to growth stimuli such as growth factors (Narita M., 2007). Various factors, including changes in physiological conditions and cellular stress, which tend to increase as organisms age, can stimulate the senescence phase.

(Itahanak etal ‹2001؛ parrinello s etal ‹2005؛ compisig ‹2005).

In fact, senescence can serve as a natural barrier or shield against aberrant cell divisions, such as those seen in cancer. Accumulated senescent cells contribute to the aging process and may contribute to the development of tumors. Cancer development can be promoted by senescent cells that appear resistant to programmed cell death, also known as apoptosis.

(Krtolica A etal, 2001; campisi J, 2003; Jackson JG and Pereira. Smith OM, 2006).

Age-related accumulation of senescent cells is also associated with organ and tissue dysfunction. Differential RNA analysis has revealed that there are differences in gene expression between senescent and youthful cells, particularly in genes implicated in cell cycle regulation. In addition, the renewal or duplication of DNA strands in pre-senescence cells becomes increasingly inefficient. (Seluanov A et al, 2004; Sedelinkova OA et al, 2004).

Age-associated cellular senescence is a crucial biological process that protects cells from uncontrolled growth and has been exhaustively characterized with age. (2004), Shay JW and Roninson IB.

"Review of References"

The aging process in humans is a complex phenomenon caused by a variety of tissue-specific alterations. Several obstacles impede the study of this phenomenon in all living organisms, including genetic variations between individuals and the inability to differentiate the effects of aging from those of maladies that occur during life (Schachter, 1998).

For over three decades, human cells grown in culture have served as a simple model for investigating the cellular process underlying this phenomenon. Haly Flick and Moorhead discovered that diploid fibroblast cells with a double set of chromosomes have a finite number of cell divisions before they cease dividing. This phenomenon was dubbed "replicative senescence." This phenomenon has also been observed in other cell types, including epithelial cells, smooth muscle cells, epidermal keratinocytes, endothelial cells, melanocyte progenitor cells, and lymphocytes (Effros, 1998).

1.2 What does replicative senescence mean?

Replicative senescence is the cessation of cell division or withdrawal from the cell cycle after a finite number of cell divisions. It is a defining characteristic of senescent cells that they remain in this

phase for months to years. During this phase, cells remain metabolically active but lose the ability to synthesize DNA (Matsumura et al, 1979).

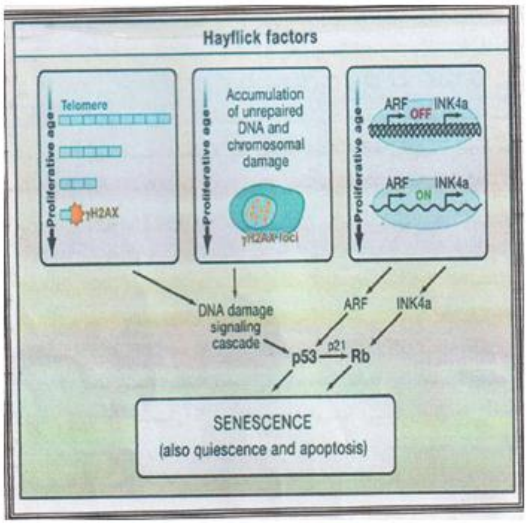
During replicative senescence, the cessation of the cell cycle is irreversible and unrelated to programmed cell death. Senescent cells undergo morphological changes, such as cell enlargement and flattening, and exhibit ambiguous expression of the senescence-marking enzyme beta-galactosidase (Dimri et al., 1995, pH6). These few indicators suggest that numerous irreversible changes occur during the senescence phase of a cell. Some immature cells exhibit analogous changes in the absence of growth factors, but these changes are reversible when the cells are dormant. Replicative senescence's role or function in organismal aging remains controversial, but information obtained from outside the living body can cast light on this phenomenon within the living body.

1. In culture, the replicative capacity of cells from elderly donors is lower than that of cells from younger donors, indicating that cells retain a finite number of double or diploid cell divisions throughout their lifetime within the body.
2. The capacity of cells to replicate is approximately proportional to the maximal lifespan of the animals from which they originated.
3. Evidence from the study of certain diseases, such as Werner syndrome (WS), which replicates premature aging in fibroblast cells obtained from individuals with WS, suggests that these cells undergo senescence significantly earlier than cells from healthy individuals (Norwood et al., 1979). The gene responsible for this phenomenon and syndrome, when cloned in bacteria, produces a protein called "WRN" that has the same properties as DNA helicase enzymes, despite the fact that most mutations occur outside the gene encoding the helicase enzyme (Yu et al., 1996).

Indeed, this suggests that the protein may have additional potential functions. There are two proposed explanations or hypotheses to account for the inability of the cell to replicate and proliferate:

First: cellular senescence is caused by the accumulation of errors, potentially as a result of compromised DNA repair mechanisms or an inability to effectively eliminate free radicals generated by cellular metabolism. Despite having the potential to regulate this process through cellular component repair or removal, these factors can have an effect on a cell's DNA, causing it to lose its ability to replicate.

Second: the lifespan of cells is governed by a genetic program that is intrinsic to the cell itself. Therefore, cellular genetic factors are implicated in the activation of cellular senescence (Nathalie G. et al., 1998).



Hayflick Limit and Replicative Senescence Factors

2.2 How do cells age and what changes occur as a result of cellular senescence?

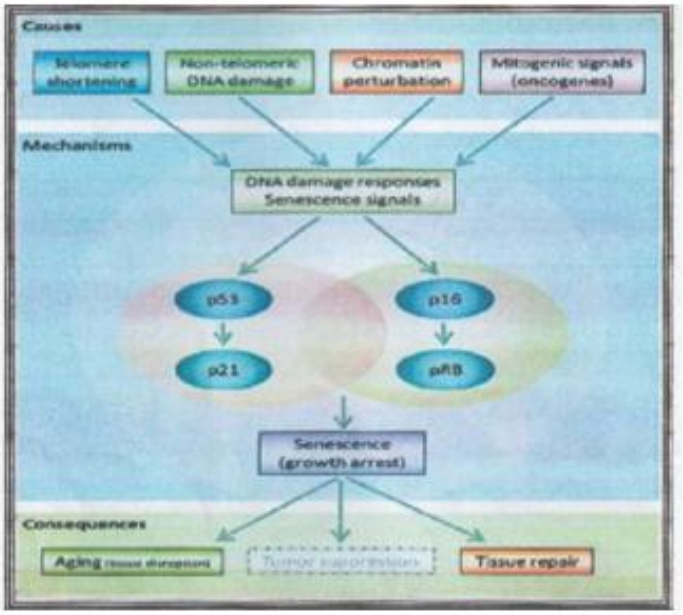
There are numerous stimuli that can induce cellular senescence in cultured human cells. The dearth of the enzyme telomerase, which is responsible for replenishing the telomere extremities of chromosomes, is the primary cause. In the absence of telomerase, telomeres diminish with each cell division by a few base pairs, eventually reaching a critical length. This is the signal for the cell to stop dividing. In contrast, cells that divide irregularly may experience an increase in short telomeres and genomic instability, which can ultimately contribute to cancer.However, even rodents cells with long telomeres experience senescence. This is believed to be the consequence of laboratory-induced tension. Moreover, the aging process causes irrevocable DNA damage in both mouse and human cells. Exposure to radiation or mutagenic compounds, for instance, can induce mutations in the DNA repair enzymes responsible for DNA damage and repair. In multicellular organisms, repairing this injury is a protective mechanism against the development of malignant tumors.

Two major proteins, p53 and Rb, mediate the regulation and control of cellular senescence. Inhibiting the cell cycle, the protein p53 plays a crucial function in gene expression regulation, DNA repair, and cell cycle arrest. A second protein, Rb, is activated by the tumor suppressor protein p16. Additionally, Rb inhibits the cell cycle in response to oxidative stress. It suppresses or inhibits genes responsible for the cell cycle, cell division, or heterochromatin stimulation (Narita et al., 2003).

The two pathways, p53 and Rb, are not wholly independent because an additional protein, p21, acts as a wide inhibitor. p21 inhibits Rb phosphorylation and can bind to MDM2, influencing p53 protein activity. The p53 pathway is predominate in rodent embryonic fibroblasts and the majority of human fibroblasts. Many human cells, however, implement the Rb pathway via p16 (Itahana et al., 2004).

Specific structural and chemical modifications take place in aging cells. The accumulation of pigment-like substances known as senility or lipofuscin granules is one of the most notable alterations. Lipofuscin is typically observed in neuronal cells and is believed to result from the oxidation of certain unsaturated fatty acids within the cell. It can also manifest in liver, kidney, and thyroid gland cells. Lipofuscin is insoluble in fat solvents and may stain intensely with fat-specific Sudan stains (Ye et al., 1996).

Normal cellular senescence, particularly in neuronal cells, is accompanied by the contraction of cell boundaries and the loss of cell translucency. There is also a discernible reduction in chromatin concentration. In addition, collagen bodies within these cells can progressively disintegrate and transform into lipid droplets, or direct cell division may also occur during this process (Gire et al., 2004).



A diagram depicting factors that contribute to aging.

3.2 Involved Pathways in Cellular Senescence:

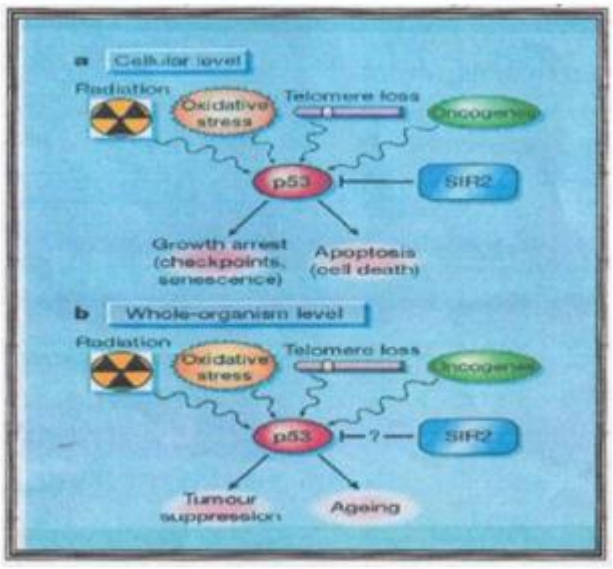
Multiple factors, including dysfunctional telomeres, non-telomeric DNA damage signals, oxidative stress, and the intensity of mitogenic signals, can contribute to cellular senescence.

Once these cellular signals have been produced, they will be activated via corresponding cell signaling pathways. These cells may enter a senescent phase or endure apoptosis, also known as programmed cell death (Collado et al., 2007). Due to the difficulty of replicating linear chromosome ends, telomere alterations are regarded as the most important mechanism leading to senescence of somatic cells in terms of replicative capacity (Harley et al., 1990; Hastie et al., 1990).

Telomeres reach a critical length and change structure after approximately 50 divisions, triggering the cell's response to DNA damage via the DNA Damage Response (DDR) pathway, which is the classical pathway (D'Adda di Fagagna et al., 2003; Gire et al., 2004; Herbig et al., 2004).

In senescent cells, DNA damage has been detected, including dysfunctional telomeres and double-strand breaks (DS). These damaged DNA molecules serve as signals to activate the p53 protein and genes that inhibit tumor growth and induce senescence (D'Adda di Fagagna et al., 2003).

Disabling the Rb and p53 genes permits further cell divisions in cells with chromosome end fusion, resulting in uncontrolled cell divisions and the development of more malignant tumors. The identical pathway may be activated to induce senescence in cells. In addition, factors such as stress, potent mitogenic signals, overexpression of cancer-related genes such as RAS, and optimal culture conditions can lead to increased expression of p16 and activation of additional tumor suppressor genes. Rb, which can bind to E2f1, can inhibit a number of genes responsible for chromatin remodeling and induce senescence in cells (Tollefsbol and Tryllefsveo, 2010).



The processes engaged in and contributing to aging.

To identify specific genes that play a crucial role in cellular senescence, a number of human cells, such as immortal or continuously dividing cells, were fused in culture medium with a variety of mutant cells. If the resultant fused cells are also immortal or capable of long-term survival, this indicates that the genes responsible for this defect are not at play. Overall, the fusion of immortal cells with multiple revertant mutants results in a predetermined number of proliferating cells that can be classified into four groups (A-D) (Smith, 1996).

The findings of these numerous tests, which involved fusing continuously dividing cells with various types of mutant cells at specified areas, led to the conclusion that at least four sets of genes are responsible for producing the phenomena of cellular senescence (Smith, 1996).

Ogata et al, discovered in 1993 that human chromosome 7 had the potential to restrict cellular divisions in cultivated fibroblast cells outside of the live organism. Ogata and colleagues discovered in 1995 that chromosomes 1, 4, and 7 include genes that encode for senescence induction or the

inability to grow in culture media. Furthermore, it was observed that chromosome 6 activates or causes senescence in one of the tissue cultures. Furthermore, Sandhu et al. determined in 1998 that other chromosomes, including chromosomes 2, 3, 10, and the X chromosome, contribute to the development of senescence in distinct tissue cultures of diverse cell types.

4.2 The Effects of Oxidative Stress on Cellular Aging:

Stress is described as an imbalance between the quantity of free radicals in the body and the defense capability of antioxidants, accompanied by an increase in lipid peroxidation, resulting in harmful damage to numerous human tissues (Betteridge, 2000).

1.4.2 Free Radicals:

One of the most significant barriers to optimum health is the existence of free radicals throughout the body. The concentration of free radicals, which include an unstable, active electron that fiercely attempts to couple with another electron to reach stability, causes oxidation in the human body. These free radicals assault any cell, nucleus, or nucleic acids within the body in order to obtain an electron or establish a stable electron pair with it. Free radicals are oxygen molecules that have had a single electron removed through chemical processes, leaving them with an unpaired electron in their outer atomic orbit, resulting in free oxygen radicals (Block et al., 2002).Free radicals are distinguished by their excitable and unstable nature, as well as their high energy and propensity for interacting with biological components within the body (Matkovics, 2003). When a cell is attacked by a free radical, it will assault another cell in order to collect electrons and achieve stability, making the second cell unstable. This cycle of cell assaults continues, resulting in continuing damage to the majority of cells. One distinguishing property of free radicals is their propensity to start a chain reaction that increases free radical production, resulting in the loss of essential molecules and cellular components in biological systems.

Because all animals and plants require oxygen for energy generation, molecular oxygen is the principal source of free radicals (Halliwell and Gutteridge, 1985). To create energy, roughly 98% of molecular oxygen is converted to water via the respiratory chain (Wohaieb and Godin, 1987). The remaining 2% of oxygen deviates from this pathway and enters a univalent pathway, where free radicals are generated (Boveris et al., 1991). Endogenous antioxidants of various sorts then neutralize and detoxify these free radicals (Halliwell, 1995).

2.4.2 Free radical Damage:

It is now known that free radicals can cause damage and degrade vital molecules in the cells of the body, including proteins, lipids, carbohydrates, and nucleic acids. The damage caused by free radicals plays a significant role in the increased production of these radicals and in a series of reactions that result in the destruction of vital molecules within the cell (Cheng et al., 2002). There are several main mechanisms by which free radicals cause damage, including:

1- Lipid Peroxidation.

Free radicals can instigate and propagate damage to lipid compounds, resulting in their decomposition and the production of additional free radicals.

2- Cross- linking Damage.

Free radicals can also induce protein cross-linking and cause oxidative damage to DNA, specifically to the ribose sugar moiety.

3- Lysosomes Damage.

Free radicals are important in the breaking of cell membranes and the release of digestive enzymes such as lysozymes into the cell, which results in the digestion and destruction of biological components.

4- Cell membrane Damage.

Free radicals may, in fact, damage cell membranes and disturb their normal permeability, resulting in

cellular function imbalances (Cheng et al., 2002).

3.4.2 The Critical Role of Free Radicals:

In addition to the health hazards associated with free radicals, these radicals also play an essential role in a number of contexts. For instance, they aid in the radiation-induced annihilation of malignant tumor tissues. In addition, they contribute to the manifestation and effects of narcotics and toxic substances. Free radicals contribute to the biological synthesis of prostaglandins by oxidizing unsaturated fatty acids in platelets and other cells through the process of lipid peroxidation. In processes such as phagocytosis and the elimination of pathogens by immune cells, they are also crucial (Atalay and El-Aaksonene, 2000).

4.4.2 The diseases caused by free radicals:

Cancer, aging, cellular senescence, gradual loss of cellular functions, atherosclerosis, Parkinson's disease, Alzheimer's disease, cataracts, complications of diabetes, liver diseases, and dental caries are diseases associated with the destructive oxidative process initiated by free radicals (Samual et al., 2000). Free radicals are also linked to maladies like white spot syndrome in poultry and a number of other conditions. Aging is a biological process that is nearly inevitable for all living organisms. As reactive oxygen species attack vital molecules in the body, causing oxidative damage and functional loss, the free radical theory is widely accepted as a prominent cause of aging (Block et al., 1996; Ballmer et al., 1994; Yu, 1996).Although the antioxidant defense system of the body, which includes antioxidants, plays an essential role in neutralizing free radicals, it may not be sufficient to eliminate all reactive oxygen species. The remaining quantity of unneutralized free radicals can contribute to the onset of senescence (Yu, 1996). Numerous studies have demonstrated that oxidative damage and lipid peroxidation levels increase with age. Demir et al. (2003) conducted a study on mice and discovered that 24-month-old mice had higher levels of hydroperoxide in their mitochondria than 12- to 6-month-old mice.

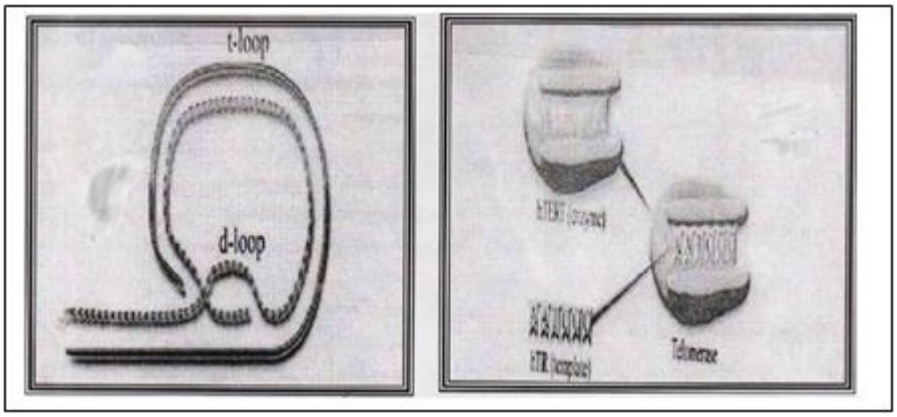
Malondialdehyde (MDA), a lipid peroxidation marker, was found at elevated levels in the livers of aged rodents, according to a separate study. Changes in polyunsaturated fatty acids were also observed in other cells of the body (Amer, 2001). In addition, proteins are vulnerable to attack by free radicals, and various tissues exhibit increased protein oxidation during the natural aging process. Moreover, the oxidative damage to nucleic acids caused by free radicals during aging results in the development of malignant tumors and the occurrence of mutations (Matkovios, 2003).

5.2 Nuclear Alterations in Aging Cells:

The nuclear changes that occur during the aging process are distinct from the cytoplasmic changes. The nucleus is more resistant to degradation and change than the cytoplasm, due primarily to its structure and chromosomal properties. During cellular senescence or aging, the nuclei of some cells may become more intensely stained than the nuclei of non-aging cells. In addition, the size of the nucleus shrinks and its structural properties deteriorate over time. These phenomena are commonly known as "nuclear pyknosis" and ultimately result in cell mortality (Share, 1998). (Lundblad, 2001) Aging nuclei are characterized by contraction, edge distortion, and a loss of clarity in their internal structures. During the nuclear pyknosis phase, there is no initial decrease in the amount of deoxyribonucleic acid (DNA) present in the nucleus. However, this decline occurs gradually as the protein content of the cell decreases. During the aging process, proteins degrade first, followed by the degradation of DNA molecules by DNA-degrading enzymes (Zentgraf et al., 2001; Riha et al., 2000). As the nucleus nears its dissolution, it loses its natural properties and begins to diminish, either prior to or in conjunction with nuclear fragmentation (Adams et al., 2001; Cunado et al., 2001; Karyarrhexis).

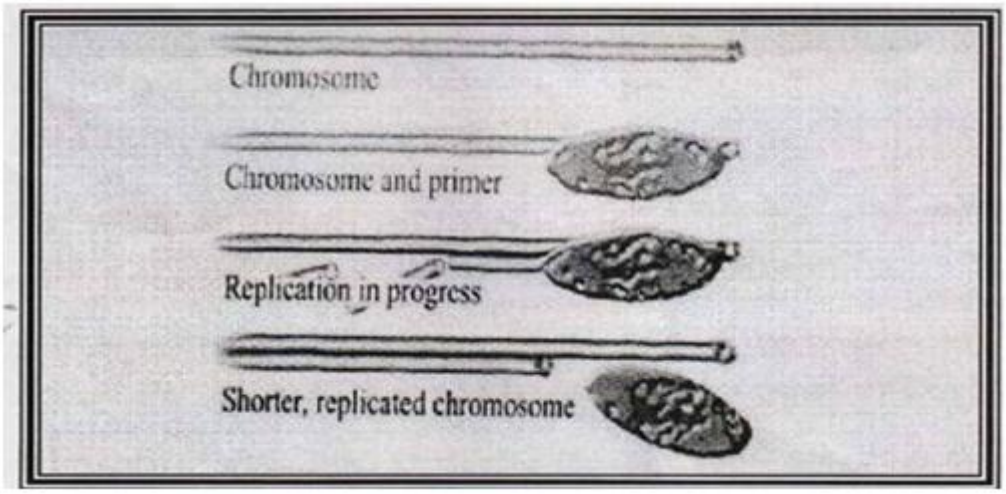
1.5.2 Telomeres and the Aging Connection:

The term "telomere" is derived from the Greek words "telos," which means "end," and "meros," which means "part" or "segment," thus "the terminal segment." Telomeres are found at the ends of each human chromosome, where they function as a protective barrier against injury. Some scientists compare telomeres to the metal cover that secures and protects the end of a shoelace (Gall, 1995).



Telomeres and Telomerase.

The terminal segment of the human chromosome is composed of a repeated sequence of nitrogenous bases (TTAGGG) (Cottschling and Stoessling, 1999). Scientists have determined the sequential structure of telomeres in humans, as well as in numerous animals, plants, and microorganisms, in recent years. None of them could have foreseen that this obviously insignificant structure signifies the "aging clock" that has plagued humanity since its inception (Bryan and Cech, 1999). Biologists have discovered that DNA polymerase enzymes, which are responsible for DNA replication during cell division, are incapable of replicating chromosomes to their extremities. They always leave a small region unreplicated at the end, resulting in a progressive reduction in telomere length (Levy et al., 1998). When the telomere length reaches a certain point of shortening, a series of sequential events within the cell lead to the cessation of cell division and the onset of senescence and cell death. Therefore, the progressive shortening of telomeres is the actual cause of cellular senescence (Maigne et al., 1999).



Chromosome End Reduction.

2.5.2 Telomerase Enzyme:

Scientists have discovered that the Telomerase enzyme is responsible for indefinitely preserving cellular vitality. This enzyme is also responsible for the cancer cells' immortality, growth, and unceasing proliferation (Kim et al., 2002). In recent years, scientists have endeavored to discover and develop contemporary medications known as Telomerase inhibitors. (Cong et al., 2002) These inhibitors are designed to prevent the activity of the Telomerase enzyme in cancer cells and restrict their divisions, which are responsible for their unceasing growth and proliferation. This creates novel opportunities for the therapy of a variety of cancers. Scientists believe that targeting the Telomerase enzyme within cancer cells is the optimal strategy for preventing the development of cancer cells, which are characterized by their potential for "immortality" and promoting their progression towards cells with a limited lifespan, resulting in aging and death.

Telomerase, the biochemical machinery responsible for DNA replication during cell division, cannot function without removing a portion of the telomere at the end of the chromosome, according to research. This gradual erosion of the telomere causes cellular senescence (Forstemann and Ling, 2001).

Simultaneously, the human cell possesses additional biochemical apparatus for compensation and repair dependent on the Telomerase enzyme, which is responsible for repairing the chromosomes' eroded telomeres. (McEachern et al., 2002) This process attempts to extend the cell's lifespan and delay the onset of senescence.

Consequently, scientists have dubbed Telomerase the "Miracle Enzyme," the "Elixir of Immortality," and the "Enzyme of Eternal Life." It is remarkable that embryonic cells, prior to the stage of cellular differentiation, routinely produce Telomerase enzyme to maintain their rapid division and compensatory abilities. However, once embryonic cells have completed their maturation, they cease producing Telomerase and the genes associated with it in most tissues, with the exception of reproductive cells (Griffith et al., 1999; De Lange, 2001).

Therefore, scientists compare the effect of silencing the Telomerase enzyme genes to the activation of a timing mechanism that regulates Telomeres and cell division in each cell lineage. Cells attain the stage of aging and mortality at a certain point (Li et al., 2000; Madder et al., 2001).

As a result, some researchers have sought to promote cell division by activating the Telomerase enzyme production. They placed the activated cells in a culture medium, and the cells began dividing constantly and energetically, full of life (Vonzaglinicki et al, 2000).

6.2 Sex and Cancer Immortality:

Except for cells that require extraordinary lifespan, our cells are not immortal and are prone to aging and death due to a deficiency of the Telomerase enzyme. As a result, the enzyme can be found in proliferative tissue cells including primordial germ cells and oocytes (Smogorzewska et al., 2000). The fact is that these cells alone have succeeded in circumventing the planned aging clock, which means that they have not turned down the genes responsible for creating the Telomerase enzyme, which is required to sustain species immortality in multicellular animals (Anceline et al., 2002).

The Telomerase enzyme, on the other hand, is extremely active in cancer cells. These cells, which were formerly normal, were able to reactivate the genes producing the Telomerase enzyme, which had been silenced since tissue cell specialization (Hott et al., 2001; Ren et al.). As a result, cancer cells have long telomeres that are constantly replenished throughout division (De Loange, 2002). This behavior is known as cancer cell destructive immortality.

7.2 Cellular Aging and Cytoplasmic Changes:

Many cells go through a period of aging that is marked by obvious disruptions in normal metabolic activities. These changes take place within the cell as a result of the action of cellular degradative enzymes, which grow increasingly active with age (Matsutani et al., 2001). These enzymes target and degrade big cytoplasmic molecules, particularly proteins.Furthermore, low oxygen levels cause non-aerobic fermentation, which results in the buildup of different acids, mainly lactic acid (Bryan, Cech, 1999). Furthermore, near the conclusion of the aging phase, the accumulation of tiny particles and ions within the aged cell produces a rise in osmotic pressure, resulting in water ingress and subsequent cell enlargement (Maigne, 1999). Cell swelling happens at this time, and protein granules develop in the cytoplasm, a condition known as hazy swelling. However, this behavior may also be generated in normal cells by some harmful agents or diseased situations (Adams et al., 2001).This state is preceded by a buildup of acids in the cytoplasm, which results in a fall in intracellular pH. Ion buildup within the cell increases water intake while also causing protein leakage into the cytoplasm in the form of small granules owing to lipoprotein breakdown (Zentgraf et al., 2001; Riha et al., 2000).

1.7.2 Alterations in Lysosomes and Their Autophagy Function with Age:

Lysosomes are the organelles with the highest capacity for degradation within the cell and are essential components of the cellular control system. Dysfunction of lysosomes disrupts cellular homeostasis and contributes to the accumulation of damaged and aberrant intracellular components, resulting in a variety of human and non-human diseases (Samantha J. and A.M. Cuervo, 2006).

1.1.7.2 Lysosomes and Aging:

Age-related changes in the lysosomal system have been observed in nearly all living organisms and tissues. Lysosomes have been identified as an additional source of cellular injury during aging. Changes in the lysosomal membrane result in the discharge of lysosomal fluid containing hydrolase enzymes, which leads to the irregular degradation of intracellular components (Kiffin et al., 2006). Given its critical role in maintaining cellular homeostasis and quality control, there has been a growing interest in understanding the consequences of the functional failure of this system in organisms in recent years. Detailed examination of different tissues in various organisms using electron microscopy has revealed morphological changes in the lysosomal system, including an increase in size, elongation of shape, altered density, and accumulation of undegraded materials, which leads to the formation of secondary pigment-like deposits known as lipofuscin (Terman A. and Brunk V, 2004).

Lipofuscin consists of lipids, carbohydrates, cross-linked protein adducts, and undegraded lysosomal material (Terman A, Brunson V, 2004). The accumulation of lipofuscin within lysosomes increases their susceptibility to oxidative injury and disrupts their pH equilibrium. This alteration impacts the permeability of the lysosomal membrane, which can result in Lysosomal Storage Diseases (LSDs) (Terman A, Brunk V, 2004). LSDs provide insight into the accumulation of undegraded products within the lysosome, which affects its functions and other cellular functions that rely on lysosomal activity (Neufeld EF, 1991).When lysosomes are unable to perform their primary degradation function, undegraded material accumulates within the lysosome. In the majority of instances, these undegraded substances endure physical and chemical alterations within the lysosomal cavity, resulting in their leakage into the cytoplasm (Neufeld EF, 1991).

2.1.7.2 Changes in Autophagy during Aging:

The autophagic capacity and decline in Chaperone-Mediated Autophagy (CMA) activity with aging are attributed not only to changes in the morphology and degradative capacity of lysosomes, but also to changes in the fundamental components of the autophagic pathway (Cuervo A.M. et al., 2005, 2006).Studies on the livers of rodents have uncovered a modification in the hormonal regulation of autophagic capacity. Through the effects of glucagon levels, which stimulate autophagy, autophagy is induced during fasting in the liver. Even under fasting conditions, decreased glucagon activity and sustained activation of insulin-independent signaling through insulin receptors contribute to decreased autophagic capacity in the livers of aged rats (Danati A. et al., 2008).

The inability of autophagic vesicles to efficiently fuse with lysosomes contributes to the decline in autophagic capacity observed in aging organisms; however, the precise reasons for this failure are still unknown (Brunk and Terman A., 2002). Intracellular pathways implicated in major catabolic processes are substantially maintained by the lysosomal degradation function. It aids in recycling or repurposing various compounds, which not only promotes positive cellular energy balance but also satisfies multiple cellular requirements for quality control, such as the removal of damaged cellular components and defense against both internal and external cellular insults. The various functions of the lysosomal system provide a clear explanation for the role of age-related alterations in lysosomes at the cellular level, which frequently contribute to disease (Wolf and Normic S.C., 2010).

3.1.7.2 Degradation of Proteins and Aging:

Scientist Stadtman E. (2001) emphasized that changes in protein composition and the accumulation of dead cells with aging are among the most prominent alterations that lead to an increase in the amount of damaged proteins in tissues and higher production rates as a result of an increase in free radical production with aging. Post-translational modifications, which occur in these proteins as a

result of oxidative damage, render them resistant to degradation by proteolytic enzymes. Changes in the side chains of amino acids, oxidation of sulfur groups, and internal isomerization of amino acids such as arginine and asparagine increase with age (HipKiss A.R., 2006). Due to the presence of free radicals, degradation resistance increases, resulting in their accumulation (Ryazanov A. and Nefsky B., 2002; Morimoto R.I., 2008).

In addition to changes in protein composition, the inability of these cells, particularly specialized cells, to proliferate and divide also contributes to the effect on cellular function and cell mortality (Cuervo A.M., 2006).

2.7.2 Mitochondrial Alterations and Their Role in Cellular Aging:

1.2.7.2 Mitochondria:

Mitochondria are organelles that are spherical or rod-shaped and found in the cytoplasm of cells. They are encompassed by a double membrane, with the inner membrane forming cristae by curling inwards. Mitochondria contain their own DNA, known as mitochondrial DNA (mtDNA), in addition to RNA and ribosomes. They are responsible for the production of the energy-storing compound adenosine triphosphate (ATP). Generally speaking, mitochondria have three primary functions:

1. The Respiratory Cycle and Oxidation.
2. Electron Transport Chain.
3. Oxidative Phosphorylation.

(Braig M et al, 2005).

2.2.7.2 Mitochondria and Aging:

During the aging process, mitochondria endure fragmentation and metamorphosis into small particles that rapidly expand and grow in size. Changes in mitochondrial permeability result in the release of apoptosis-inducing factor (AIF). Experiments have demonstrated a decrease in the rate of mitochondrial protein synthesis (Chen et al., 2001). Additionally, there is an increase in the production of reactive oxygen species (ROS) per unit of mitochondrial mass, such as hydrogen peroxide (H2O2) and superoxide radicals.

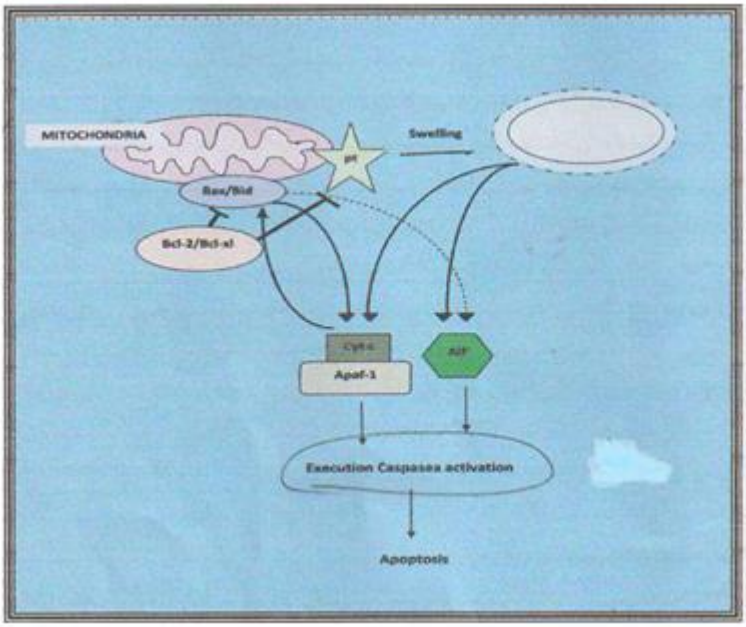
ATP (Degrey, 1997; Lee and Wei, 1997). The functionality of mitochondrial DNA (mtDNA) decreases with age and it endures mutations (Allen et al., 1999). Coron et al. (1981) and Ander Son et al. (1979) confirm that the extent of damage to mitochondrial morphology and chromosomal state differs among species. Due to reactive oxygen species, depletion of protective histones, and a lack of introns, mtDNA is damaged 20 times more frequently than chromosomal DNA (Coron et al., 1981; Ander Son et al., 1979). Experiments have revealed that mitochondria contain a KD-50-molecular-weight protein that is released through permeability transition (pt) pores. This protein was named apoptosis-inducing factor (AIF) derived from mitochondria after its function in the changes that occur during programmed cell death, such as chromatin condensation and DNA fragmentation, was revealed by its isolation (Dobson et al., 2000).

Susin et al. (1996) discovered that the encoded protein 2-Bl in mitochondria protects cells from AIF leakage, thereby preventing aging by retaining the apoptotic protein AIF within mitochondria.

At multiple levels of cell death signaling pathways, mitochondria play a crucial role in determining whether cells will remain intact or incur cell death.

1. Level one: Mitochondria can accelerate aging by increasing the generation of reactive oxygen species (ROS).
2. Level two: Mitochondria will govern the efficiency of cell death processes via protein family members such as 2-AIF, execution caspases, Cytochrome C, and Bcl.

(Datta et al, 1997; De Lpeso et al, 1997).



Changes in mitochondria cause aging and programmed cell death.

8.2 Environmental and Genetic Factors Influencing Cellular Aging:

Is natural aging regulated and controlled by a biological clock within our cells, or is it the product of degenerative processes that harm our cells as a result of exposure to numerous environmental factors? Aging is most likely caused by a combination of hereditary and environmental factors. The length of telomeres, which is a hereditary feature, is a significant element in aging (Karl Seder et al., 2002). However, what is the point of having long telomeres if they are prone to fast destruction as a result of environmental risk factors, necessitating repair and subsequent cell division? Rapid telomere shortening, on the other hand, causes cellular, tissue, and organ aging (Griffith et al., 1999). It is likely that premature aging is induced by environmental variables that accelerate the formation of damaging free radicals rather than inherited significantly short telomeres from parents (Faragher et al., 1997). According to research on fruit flies, the majority of mutations that postpone aging occur in genes that suppress the formation of free radicals (Rawes et al., 1997). In other words, protecting against free radical damage is a crucial element in delaying cellular aging.

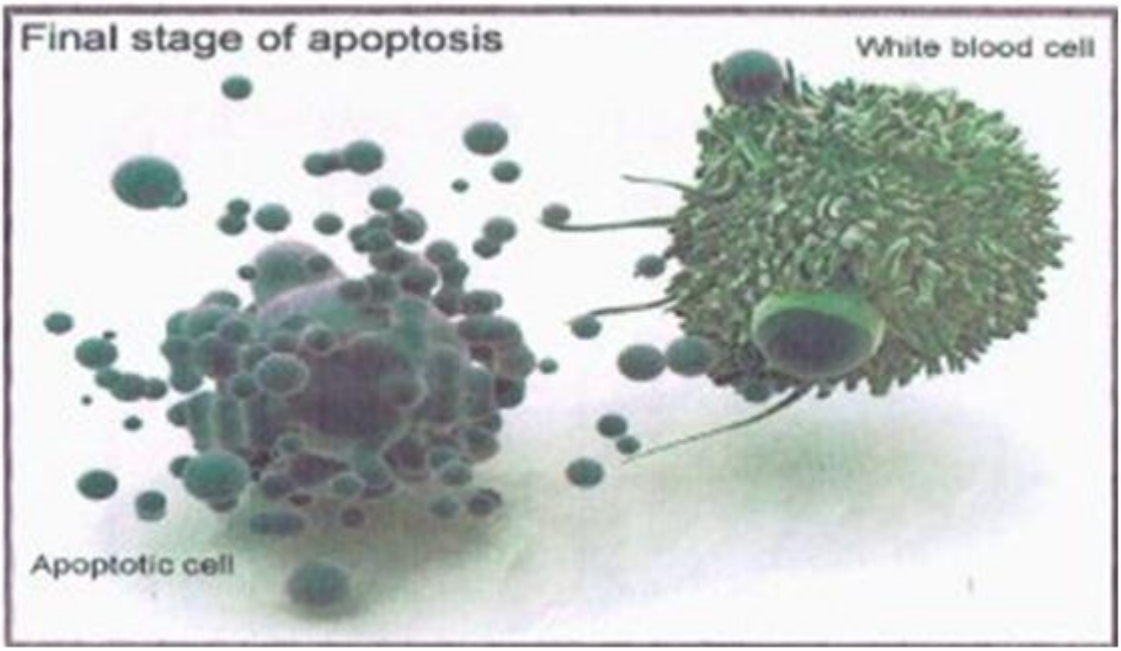
Scientists ascribe variances in lifespan across species and age differences between persons to telomere length variations (Seimiye and Smith, 2002). Furthermore, telomere lengths change amongst tissue cells in the body. The telomeres of vein lining cells, for example, are usually longer than those of artery lining cells. This is owing to artery cells being subjected to more rigorous stress and damage than vein cells, necessitating more repair mechanisms, more cell division, and shorter telomeres in arterial cells. As a result, arterial cells show indications of aging faster than vein cells (Burkle, 2002; Cook et al., 2000). As a result, people frequently complain about hardened arteries rather than hardened veins.

9.2 Apoptosis, or programmed cell death:

A cell's aging process eventually leads to its death. The broad definition of cell death is the total termination of its essential processes. "Catabiosis" refers to the changes that occur in the cell as it ages, culminating in death and the collapse of life (Singer and Berg, 1991).

Certain agents or chemicals that promote abrupt freezing or deposition of cytoplasmic material, as seen when tissues are exposed to heat, can expedite cell death (Pandita, 2002). In a natural way, the critical functions within the cell come to a standstill. The cell may sustain irreversible damage but continue to function for a time. For example, when cells are crushed, their outer edges may tear, but they continue to perform biological processes such as oxygen consumption, fermentation, or membrane breakdown for a short time before cessing completely (Counter et al, 2000; Amit et al, 1992). The last coagulation of the cytoplasm is a phenomena that happens following cell death. This

event can last for a long time before the cells are digested and dissolved (Spring et al, 1997). The nucleus also loses its inherent characteristics and disintegrates (Adams et al, 2001). Dead cells can be identified with important stains such as Neutral Red, Methylene Blue, and Janus Green. The cytoplasm of dead cells looks thickly stained, but the nucleus of living cells appears more powerfully stained (Adams et al, 2001).



The most advanced level of programmed cell death.

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