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Cellular Senescence and Its Relation with Telomere

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1. Introduction

For years it was thought that cells under culture conditions were immortal; however, from the publication of the works of Leonard Hayflick, this concept changed. Hayflick demonstrated that somatic cells under culture conditions had a limited capacity to proliferate; they stop dividing and enter into permanent arrest in the cell cycle, known as senescence. A particular characteristic of this state is that the cell maintains its viability and metabolic activity, and despite the presence of nutrients and mitogens, it does not divide (Ouellette et al., 2000). There are reports of cells that have been maintained in this state during several decades (Michaloglou et al., 2005). Regarding the origin of this process in mammalian cells, two different and apparently contradictory hypotheses have been proposed: senescence as a mechanism that suppresses tumor development, and senescence as the loss of the cells' regenerative capacity *in vivo*. In terms of the first hypothesis, senescence possesses a beneficial effect for the organism because it would avoid the development of cancer; otherwise, the second hypothesis would exert a harmful effect on organisms in that it would favor aging. Commentary will appear later on that both hypotheses joined together in the antagonist pleiotropic hypothesis (Williams, 1957; Campisi & Adda di Fagagna, 2007; Campisi, 2011).

2. Hayflick experiments

It was 50 years ago that Hayflick first reported on the condition of mortality that cells maintain (Hayflick & Moorhead, 1961), which the researcher himself cited in 1998 (Hayflick, 1998). To the present day, few have dared to enter into the study of Biogerontology. The generalized belief was that cells kept under culture conditions could replicate themselves indefinitely; if this were not possible, it would be due to lack of knowledge on the appropriate conditions for maintaining cells under culture (Hayflick, 2003). Carrel in 1921 stated that it was possible to keep chicken-heart fibroblasts indefinitely, maintaining these with embryonic tissue extract. However, as Hayflick noted, this experiment involved a great

technical error because the extract with which the culture was nourished throughout 34 years was supplied with fresh cells throughout the entire time that the experiment lasted (Hayflick, 1998).

Hayflick identified three phases in his cellular proliferation experiments: phase I or that of primary culture, in which cells initiate their proliferation; phase II, that of rapid and continuous proliferation, and phase III, in which proliferation velocity diminishes and is finally detained (Hayflick & Moorhead, 1961). Hayflick concludes that cells possess some type of counting mechanism because they stop dividing after a certain number of duplications, between 40 and 60. This counting mechanism is conserved even after the cells are frozen and cultured anew (Hayflick & Moorhead, 1961; Hayflick, 1965).

Some years later, thanks to the work of McClintock on chromosomal ends (McClintock, 1941), Olovnikov formulated his theory concerning the problem of replication and the solution to this. Suggesting that the inability of polymerase to replicate chromosomal ends totally was what could lead to cellular senescence, he proposed that the ends could function as a buffer, avoiding the loss of important sequences, but that in turn, this buffer function could also could be lost with successive replications (Olovnikov, 1996). Later, with the discovery of the telomeric repeats sequence of and telomerase by Blackburn, the study of telomeres and their participation in the senescence process began.

Currently, the existence is accepted of a limit of normal somatic cell replication, denominated the Hayflick limit. However, once the importance is established of telomerase as the enzyme that synthesizes telomeres (Greider & Blackburn, 1985), it was discovered that this enzyme is found to be active in immortalized cell lines (Morin, 1989), tumor cells (Kim et al., 1994), stem cells (Chiu et al., 1996), and embryonic and germinal cell lines (Mantell & Greider, 1994; Wright et al., 1996).

3. The antagonistic pleiotropy hypothesis

Antagonistic pleiotropy is a concept pertaining to Evolutionary Biology that proposes that some genes can have an impact on the physical state of the organism differentially throughout its lifetime (Williams, 1957; Tuminello & Han, 2011). It is suggested that senescence evolved as an example of antagonistic pleiotropy; thus, its characteristics are beneficial in a reproductively active organism; later in this organism's lifespan, these characteristics become deteriorating. That is, senescence is the result of the random accumulation, whether passive or active, of harmful mutations (Kirkwood, 1977), reducing vigor and longevity, after the individual has passed reproductive age (Walker, 2011), although there is no definitive evidence that supports the negative effect of senescence in old persons.

Diverse processes have been found that are considered examples of antagonistic pleiotropy. Inflammation is a vital process to fight against infections and for cicatrization at all ages, but is also a process that can have negative effects if it becomes chronic in old age (Hornsby, 2010). On analyzing the influence of TP53 polymorphisms on cancer with respect to age, Cherdyntseva et al. (2010) found a relationship between the presence of polymorphisms in both genes and the increase of the risk of lung cancer in young, but not in older, smokers,

while the combination of wild-type alleles increased the risk of lung cancer in individuals aged >60 years. The researchers concluded that p53 protects the organism against cancer at the beginning of life, but that it promotes the aging phenotype in older persons, including the appearance of cancer at the end of life. Another recent study suggests that allele ε4 carriers enjoy a beneficial cognitive effect in youth, and that later at an advanced age present cognitive diminution, which could increase the risk of presenting Alzheimer disease, although it could be that this allele is not pleiotropically antagonistic, but rather that it interacts with other risk factors for Alzheimer disease (Tuminello & Han, 2011). Feltes et al. (2011) suggest that aging and age-associated diseases could be the result of a program of development that is activated from the embryo stage, that persists throughout life, and that is regulated by the interaction of protein networks that connect environmental with molecular signals. The protein networks of the immune system, the epigenetic network, and aerobic metabolism are subject to great selection pressure during embryogenesis. However, this pressure becomes more relaxed in the adult, which allows the initiation of aging-associated diseases.

4. Somatic cells and senescence

After gametes are fused during the fertilization process, that primordial cell denominated the zygote begins a long journey in the formation of the individual. However, this journey begins with an accelerated expansion in the number of cells, which later decelerates. Once the organism has been formed, it will utilize cellular replication during its entire lifetime to grow, regenerate its tissues, cure wounds, or during the immune response.

Somatic cells possess a limited number of possible cell divisions, after which these become refractory to mitogeneic stimuli and enter into replicative senescence. In 2001, Sin et al. cite that aging at the cellular level is the result of cell function alterations, such as the response to DNA structural changes that is reflected in the expression of genes. A senescent cell remains arrested at cell cycle stage G1, and although it does not divide again, it remains metabolically active for a long time. The accumulation of mutations and damage to the DNA, together with inefficient repair mechanisms, become critical with each cell division and cause genetic heterogeneity in aging cells (De, 2011). There are somatic cells that possess the capacity to renew themselves, such as epithelial and blood cells, while there are cells that once differentiated, do not divide again, such as neurons. The equilibrium in death maintains homeostasis in the individual; thus, excessive death can lead to tissue degeneration and the inability to die can lead to hyperplasia and finally, cancer. The accumulated errors in a senescent cell's DNA can alter this balance and cause diverse diseases (Hotchkiss et al., 2009).

5. Senescent phenotype

To date, there is no senescence marker that is totally specific for this stage because not all senescent cells express the same markers. These cells can exhibit diverse changes that in their entirety can aid us in defining the senescent phenotype (Rodier & Campisi, 2011).

Change in cell volume is one of the most evident characteristics of a senescent cell, because cells may be observed that range from 1,000 μm² in an early passage of human fetal

fibroblasts up to 9,000 μm² in terminal passages of the culture. Size increase has been correlated with changes in cytoskeletal organization (Wang & Gundersen, 1984), which leads to modification in cell shape. For example, fibroblasts lose their typical tapered form to acquire a flat appearance (Greenberg et al., 1977), apparently due to changes in the expression of diverse cytoskeletal proteins. Nishio et al. (2001) found that senescent fibroblasts contain three times the amount of the cytoskeletal protein vimentin as embryonic fibroblasts. Vimentin presents as dense filament bundles that are parallel to the longest cell-body axis in senescent cells, while in young cells vimentin formation is observed as a network of short and thin filaments. The authors also demonstrated that young fibroblasts acquire a senescent phenotype once they are transfected with a vector that over expresses the vimentin gene, while actin levels diminish in senescent fibroblasts (Nishio & Inoue, 2005). This diminution causes rigidity in old donor cells and increases in the kinesis of cell reorganization (Zahn et al., 2011). On the other hand, cellular adhesion of aging fibroblasts increases. It was found recently that the senescence of vascular epithelial cells induces an increase in cell adhesion proteins, which in turn increases the adhesion of monocytes to endothelial cells through their binding with Intracellular adhesion molecule 1 (ICAM1), contributing to the appearance of atherosclerosis (Yanaka et al., 2011).

Another characteristic of cellular senescence is change in diverse organelles; a very common occurrence comprises the increase in lysosome number and size. In lysosomes, granules of lipofuscin, the so-called aging pigment, accumulate (Brunk & Terman, 2002; Gutteridge, 1984). This material cannot be degraded by the cell's proteolytic machinery, is highly toxic, and inhibits the degradation of oxidized proteins (Bader et al., 2007; Höhn et al., 2011). Another lysosome-linked senescence biomarker is β-galactosidase, which is derived from the β-D-galactosidase and whose activity increases in senescent cells. In non-senescent cells, lysosomes possess a pH4-optimal function, while when the cell ages, the lysosomal compartment expands and β-galactosidase increases; thus, it is possible to detect a suboptimal pH of 6, a change known as senescence-associated β-galactosidase activity (Dimri et al., 1995; Lee et al., 2006). Senescence is also implicated in the deterioration of mitochondrial function and in the appearance of mutations in mitochondrial DNA, due to the lack of a repair system (Percy et al., 2008), and it is considered that aberrant production of Reactive oxygen species (ROS) can increase the mitochondrial mass (Hwang et al., 2009) and on the other hand accelerate telomere shortening and contribute to cellular aging (Liu et al., 2002) due to damage to the DNA. With respect to the nucleus, the increase in chromatin condensation is the most evident nuclear change. Regions are formed that are known as Senescence-associated heterochromatin foci (SAHF); these DNA regions are associated with heterochromatin proteins such as HP1 and H3K9m (Narita et al., 2003). SAHF are also evident in cells that become senescent because of oncogenic stress with H-Ras (Kosar et al., 2011).

Changes in senescent cells are also reflected in their functions; for example, fibroblasts under culture conditions adopt a matrix-degrading phenotype, while adrenal cortex epithelial cells produce an altered steroid-hormone profile (Campisi, 2000). Due to the increase in the secretion of pro-inflammatory proteins such as interleukins and chemokines, it is said that senescent cells are found in a pro-inflammatory state (Freund et al., 2010), which in an aging organism can favor tissue deterioration.

5.1 Changes in gene expression, growth arrest, and apoptosis resistance

Cell cycle arrest-associated replicative senescence is related with telomere shortening and, as previously noted, is a response for suppressing tumor formation and that can have aging of the organism as a side effect (Harley et al., 1990; Campisi, 2011). The cell population gradually stops dividing. (Thomas et al., 1997). Cell growth inhibition can be the result of cellular quiescence, whether due to lack of growth or nutrient factors or to other in- and extrinsic factors. This leads to the cell's exhibiting a low metabolic rate, low protein synthesis and cell functions, and the absence of growth (Blagosklonny, 2011). The senescent cell is defined by the permanent lack of replicative potential despite receiving a mitogenic stimulus (Rodier & Campisi, 2011). The cells remain arrested in G1, although on some occasions can be stopped in G2 (Harley et al., 1990). The central signaling pathways for senescence are represented by the p16-pRb Retinoblastoma (Rb) protein and the p53 tumor suppressor (Lowe & Sherr, 2003). The p14-p53-p21 pathway is partially telomere-dependent, while the p16-pRb pathway is independent of the presence of dysfunctional telomeres (Campisi & d'Adda di Fagagna, 2007). The product of *p53* gene accumulates in response to cellular stress, which activates a specific gene target program to restrict the growth of abnormal or damaged cells; the result can be apoptosis, transitory cell cycle arrest, or permanent arrest (Beausejour et al., 2003). Thus, the product of *p53 gene* possesses anti-cancerous as well as pro-aging effects depending upon the context of the individual's age (Campisi, 2005). Among p53 target genes are found the Cyclin-dependent kinase (CDK) inhibitor p21, the pro-apoptotic genes *BAX* and *APAF1*, and the E3 ubiquitin ligase, MDM2 (Vousden & Lu, 2002). *p53* expression is controlled by p19 (Arf). On the other hand, Rb expression is controlled by p16Ink4a, whose protein levels increase in senescent cells. p16Ink4a maintains pRb in a hypophosphorylated state, which inhibits cell proliferation and induces growth arrest through the pRB effect on E2F; this is necessary to activate the genes implicated in cell cycle progression (Campisi & d'Adda di Fagagna, 2007). Both signaling pathways interact and are reciprocally regulated. However, each can interrupt the cell cycle independently.

As Blagosklonny (2011) cites, cell arrest is only one part of the senescence equation, because senescent cells also become resistant to apoptosis. There are mechanisms of defense that augment apoptosis resistance, increasing anti-apoptotic signaling and avoiding the death of damaged cells. The increase of apoptosis resistance is a cell safety mechanism, because if cells have an acute stress due to some damage, they possess the capacity of recovering their homeostasis. However, in aging, when stress becomes persistent apoptosis resistance can cause the survival of undesired cells (Hampel et al., 2004; Salminen et al., 2011). It has been observed that the equilibrium between apoptotic and pro-apoptotic proteins changes with age. Bcl-2 and Bcl-xL protein levels are higher in aging than in young fibroblasts, while pro-apoptotic Bax levels are higher in young cells (Rochette & Brash, 2008). Apoptosis markers such as FasL and cytochrome C decrease in serum and, on the other hand, levels of soluble Fas (an apoptosis inhibitor) increase (Kavathia et al., 2009). Salminen et al. (2011) suggest that apoptosis resistance can affect the host's defenses in age-related fashion, a situation that meets promoted by the chronic inflammation that senescent cells develop.

6. Senescence markers

There are some molecular senescence markers that are characteristic of damage to DNA, including the nuclear foci of phosphorylated histones H2AX and DNA damage response

factors such as 53BP1, MDC1, and NBS1 (d'Adda di Fagagna, 2008), which explains why culture shock can trigger senescence without the participation of telomeres. p16 is used for identification of senescent cells due to that it is overexpressed in the majority of these cells (Krishnamurthy et al., 2004). Although it has been demonstrated that in *Caenorhabditis elegans* alterations in microRNA´s (miRNAs) expression are associated with aging, the role that these could play in mammals remains unknown. In *C. elegans*, lin-4 over expression leads to an extension in its life span, while loss of lin-4 reduces the life span (Boehm & Slack, 2005). Lin-4 acts on the lin-14 messenger, affecting not only the life span, but also the insulin signaling pathway (Hung et al., 2010).

7. Causes of cellular senescence

In stem cells, it has been observed that premature differentiation and senescence are alternatives to DNA damage repair that can exert a beneficial effect on restricting the accumulation of defective stem cells. However, sensitivity to DNA damage and p53-related apoptosis induction differ widely among stem cells (Blanpain et al., 2011). The stem cells of melanocytes, for example, undergo premature differentiation, which reduces the stem cell pool and causes graying of the hair (Inomata et al., 2009). On the other hand, loss of TP63 (a member of the p53 family) in dermal precursors leads to skin ulceration and cicatrization defects due to genomic instability and the induction of senescence (Su et al., 2009).

Recently, a chromatin remodeling factor was found to be implicated in replicative senescence, the Jun 2 dimerization protein (JDP2), which binds to histones and inhibits the binding of Polycomb repressor complexes (PRC1 and PRC2) to p16 gene promotor (Huang et al., 2011).

7.1 Telomere-induced senescense

The loss of proliferative potential can be a genetically programmed process. The telomere-associated aging theory suggests that progressive telomere sequence loss triggers chronic p53 activation, which consequently leads the cell to halt its proliferation (Lee et al., 1998). Telomere shortening is a stochastic event; thus, telomere length varies greatly among individuals (Halaschek-Wiener et al., 2008).

Dysfunctional telomeres trigger the response to DNA damage, which includes activation of ATM, 53BP1, Mdc1, Chk2, and H2AX, in addition to over expression of cell cycle inhibitors p21Cip1/Waf1 and p16INK4a and under expression of different cell cycle proteins (Herbig et al., 2004).

7.2 Senescence induced by non-telomeric chromatin alterations

Non-genotoxic stress can cause perturbations in chromatin, that is, epigenetic changes that can alter the genetic schema of the cell. It has been demonstrated that global genome methylation diminishes with age. However, it has also been observed that the promoters of certain genes can be hypermethylated, thus silenced. Histones themselves undergo modifications during aging, whether because of methylation or hypoacetylation; all of these chromatin regions in senescent cells are observed as transcriptionally inactive domains

(SAHF) (Funayama, 2007). One characteristic of the senescence program is observed in cultured fibroblasts in chromatin reorganization through H3 methylation in the Lys9 residue and by protein recruitment in the heterochromatin. Some agents that interact with DNA, such as doxorubicin, cisplatin, taxol, vincristine, cytarabine, and etoposide, can produce the senescent phenotype in tumor cells (Chang et al., 1999).

It has been suggested that the condensation of genes implicated in proliferation through SAHF formation can contribute directly to senescence-associated silencing. However, it was recently suggested that SAHF are the result of persistent damage to the DNA and that it is condensation of the genes that promote proliferation, to a greater extent than large-scale SAHF, which detains senescence-associated proliferation (Rai & Adams, 2011).

7.3 Senescence induced by stress and other factors

Cellular senescence can additionally be induced prior to telomere shortening, which is also known as premature senescence or stress-induced premature senescence. One example are fibroblasts under culture, which are exposed to stress by abnormal concentrations of nutrients and growth factors, in addition to the absence of neighbor cells and extracellular matrix, which can lead to the senescent phenotype (Sherr & DePinho, 2000). It also results from exposure to mutagens, such as ionizing radiation, ROS, chemotherapeutic agents, or bacterial toxins (Campisi & d'Adda di Fagagna, 2007); thus, the molecular mechanisms of induction are nearly identical to replicative senescence, that is, it is mediated by ATM-p53-p21. Another type is oncogene-induced senescence (Vavrova & Rezacova, 2011). However, it has been observed that moderate stress leads to telomere shortening and that the main cause of shortening is due to the presence of damaged bases, which interferes with the replication fork in telomeres, increasing the extension of the non-replicated ends (von Zglinicki, 2002; Duan et al., 2005). Non-genotoxic stress induces senescence by means of a telomere-independent mechanism, which involves p16-pRB pathway activation by $p16_{INK4a}$ over regulation (Ben-Porath & Weinberg, 2005).

Matos et al. (2011) recently analyzed the role of copper in inducing senescence in WI-38 fibroblasts and found that on exposing these to subcytotoxic copper sulfate concentrations, the fibroblasts exhibited the appearance of the senescent phenotype and an increase in senescence-associated genes such as *p21*, *apoJ*, fibronectin, *TGF β1*, *IGFBP3*, and Hemo oxigenase-1 (*HO-1*). These results are interesting because of the participation that copper can have in the establishment and progression of diseases such as Alzheimer and that of Wilson. On the other hand, it is possible that oxidative stress produces telomere shortening, therefore senescence, as confirmed by Brandl et al. (2011), because on exposing articular chondrocytes to oxidative stress with a sublethal dose of H_2O_2, the authors observed accelerated telomere exhaustion with over regulation of p21 expression and sub expression of SIRT1 and XRCC5, once the cells had acquired the senescent phenotype. Cellular senescence also can be induced by stress in the cultured cells, such as continuous mitogenic stimulation (Serrano & Blasco, 2001). Sustained exposure of melanocytes to an aberrant mitotic stimulus causes senescence after an initial proliferative burst, such as that observed by Michaloglou et al. (2005) suggesting that oncogene-induced senescence represents a factor of protection against cancer.

8. The mammalian telomere

Telomeres are restricted to chromosomal ends and present in eukaryotes as diverse protozoans, fungi, flagellates, plants, and animals. The greater part of telomere DNA is double-stranded; however, the terminal 3′ end is single-stranded. Each telomere is composed of a great region of short repeats rich in G. The sequence comprising a telomere varies in length and complexity depending on the organism (Greider, 1996). In the case of humans and other mammals, the sequence is TTAGGG, while organisms such as yeasts possess irregular repeat sequences in which a T is followed by one, two, or three Gs (TG_{1-3}), while other organisms lack A in their repeats, as occurs in the ciliate Tetrahymena, which presents the TTGGGG sequence, and the Paramecium, which is distinguished by the TTGGGG and TTTGGG alteration.

Telomere DNA consists of two regions: one is double-stranded, and the other is single-stranded at its terminal end. The G-rich chain is that which projects further than the C-rich chain in the 3′ direction. This salient is essential for telomere formation, due to that linear chromosomes need to protect their ends from degradation. The 3′-OH salient invades double-stranded telomere repeats, forming a loop-like structure called the T-loop (Telomere loop), in such a way that the salient remains hidden in the double chain (Griffith et al., 1999). The T-loop avoids that the ends are considered as DNA breaks and preserves genome integrity. The exact structure of the T-loop's base is unknown, but there is a short, double-stranded DNA segment that forms a D-loop (Displaced loop) of TTAGGG repeats, which is displaced by the invasion of the 3′ salient (De Lange, 2002). The D-loop region can include Holliday-type binding (the intermediate state in homolog recombination) or a quadruple G fold (Neidle & Parkinson, 2003). The 3′ salient, which in humans is between 35 and 600 nucleotides long, is the result of the impossibility of replicating the last fragment of Okasaki and of post-replicative processing events (Stewart et al., 2003).

9. The shelterin

Maintenance of telomeric structure and regulation of its functions are supplied by diverse proteins that stabilize it and that permit the cell to distinguish between a natural chromosomal end and a DNA break. Shelterin or Telosome is a six-protein complex whose function is to form and maintain the T-loop. TRF1 and TRF2 are the main shelterin proteins. TRF1 modules telomere length, while TRF2 stabilizes T-loop structure (Xin et al., 2008). Other proteins have been described that, in addition to associating with the telomere, possess other cellular functions, such as XRCC5, which participates in double-stranded DNA damage repair (Thacker & Zdzienicka, 2004). SIRT1 is a negative regulator of p53 and that which avoids growth arrest, senescence, and apoptosis (Guarente, 1999). Double-stranded telomere DNA is wrapped in protein complexes that specifically bind to double-stranded proteins and that participate in the regulation of their length, while the 3′ salient is wrapped in one or more single-stranded binding proteins that protect it (McEachern et al., 2000). The TRF protein family has a similar architecture, defined by two characteristic sequences: both have a DNA-binding motif in their helix-turn-helix carboxyl-terminus (highly related with the Myb domain of cMyb), and both possess a centrally localized sequence motif known as the TRF homolog domain (TRFH), unique for this protein family, which allows it to form homodimers (Fairall et al., 2001). However, the TRFH domain does

not form heterodimers, which leads to the presence of two protein complexes on the telomeres: one formed through TRF1, and the other by means of a paralog, TRF2 (Karlseder, 2003). TRF1 forms homodimers in order to bind stably to the DNA thanks to its Myb domain and, by means of T-loop formation, its binding with Rap1 at telomere repeats induces superficial double-strand folding, which indicates that it participates in loop formation (Bianchi et al., 1999). In cis, TRF1 acts in as a negative telomere length regulator. Its over expression produces telomere shortening and a dominant negative allele produces inappropriate lengthening in such a way that the amount of protein affects telomere size (Smogorzewska & de Lange, 2002). TRF1 can control telomerase access through its interaction with proteins TIN2, PTOP/PIP1, and POT1 and regulates their activity on interacting with PINX1 (Zhou et al., 2001). It also binds to TANK1 and 2 (Smith et al., 1998). Elimination of TRF1 produces telomere lengthening, but the extension stabilizes eventually due to that now the TIN2/TINT1 complex associates with TRF2, blocking access to telomerase (Houghtaling et al., 2004).

On the other hand, the complex formed by TRF2 is particularly important for protecting single-strand of the degradation and DNA repair processes (van Steensel et al., 1998; Smogorzewska & De Lange, 2004). TRF2 couples in the binding between double- and single-stranded repeats to facilitate T-loop formation, thus protecting its ends. In this manner, it is responsible for linear telomeric folding for T-loop formation (Griffith et al., 1999) and is found in >100 copies per chromosome (de Lange, 2002); additionally, given that it is the stabilizer of this structure, a lesser amount of TRF2 leads to T-loop opening, an event that can lead to senescence (Karlseder, 2003). Additionally, loss of TRF2 activates the Ataxia-Telangiectasia protein (ATM) kinase pathway, because while this is present it impedes autophosphorylation. ATM activation leads to p53 over regulation and G1/S arrest by means of p21 (Karlseder et al., 1999). When this is displaced from the telomere employing a dominant negative allele, the cell loses its ability to recognize the difference between a natural DNA end and a broken end. On the other hand, its over expression accelerates telomere shortening, which can be the result of the increase in the activity of a nuclease, whose activity is mediated by TRF2 (van Steelsen et al., 1998); Karlseder et al. (2002) suggest that an increase in TRF2 can protect critically short telomeres, delaying induction of cellular senescence even when the telomeres have been reduced. It can protect the single chain indirectly on recruiting Pot1.

It can bind to proteins such as Rap1 and to others involved in DNA damage repair responses, such as the MRE11/RAD50/NBS1 complex, Ku86, and ERCC1/XPF. Among its activities in blocking DNA repair is found that of avoiding that the T-loop insertion site is treated as a Holliday structure. On the other hand, inhibiting the binding of Non-homologous end-joining (NHEJ) and homologous recombination in telomeres and probably in non-telomeric breaks allows determination of which repair pathway the cell should use (Wright & Shay, 2005). On the other hand, TRF2 facilitates the degradation of telomeric DNA on interacting with the WRN exonuclease, whose loss-of-function is implicated in premature cellular senescence, increasing the frequency of cancer and genomic instability (Machwe et al., 2004).

There are diverse proteins that bind indirectly with telomeres; TIN2 has emerged as an important component of the telomere complex. It interacts with the telomere through the

TRFH domain of TRF1, negatively regulating telomere length. A truncated form of TIN2 produces abnormal telomerase-independent telomere lengthening; therefore, it is a TRF1-function mediator on potentiating the pairing of telomere repeats in a TRF1-dependent manner; in addition, it can lead to the telomerase-inhibiting telomere (Kanoh & Ishikawa, 2003). In addition to this telomere-size regulator function, another mutant form generates DNA damage response and senescence (Kim et al., 2004). Through this protein, TRF1 and TRF2 can interact, while TIN2 can stabilize TRF2-complex binding to the telomere on acting as a liaison between this and TRF1. On the other hand, thanks to its third domain, it binds to PIP1/PTOP/TINT1, which in turn serves to recruit POT1 (Liu et al., 2004; Ye & de Lang, 2004). On controlling the Poly (ADP-ribose) polymerase (PARP) activity of tankirase 1, TIN2 protects TRF1 on its removal from the telomere (Ye & de Lang, 2004).

Tankirase 1 interacts with the TRF1. It is a PARP telomere that adds poly ADP-ribose to TRF1, diminishing its affinity for telomeric DNA (Smith & de Lange, 2000). More than diminishing TRF1 affinity for telomere repeats, what TANK1 does on separating TRF1 from the DNA is to expose its myb domain, which is recognized and marked by ubiquitin, leading to degradation of the protein by the proteosome. If this were performed otherwise, TRF1 would bind again to the telomere and its separation would permit the telomerase to gain access to and extend it (Chang et al., 2003). TIN2 is what stabilizes TANK1 binding to the TRF1 complex, and although TANK1 is the lesser abundant of these two proteins, it is necessary for controlled dismantling of the telomere complex during S phase (Ye & de Lange, 2004).

TANK 2, recently identified as a Golgi-associated protein, shares 80% identity in the amino-acid sequence with TANK1, in addition to similar distribution; however, when this is over expressed, it induces rapid cell death with necrotic characteristics (Kaminker et al., 2001). In addition and similar to TANK1, it is a PARP modifier of TRF1 and possibly possesses little effect on telomerase activity (d'Adda di Fagagna et al., 2004).

There are a variety of other proteins that bind to telomeres, such as Ku, Rap1, PIP1/PTOP/TINT1, WRN, PINX1 (Stellwagen et al., 2003; Espejel et al., 2002; Kanoh & Ishikawa, 2003; Köning & Rhodes, 1997; Lei et al., 2000; Ye & de Lange, 2004; Crabbe et al., 2004), and ATM. On the other hand, repair-machinery proteins such as the Mre11/Rad50/Nsb1 complex (the MRN complex), which participates in double-stranded DNA repair, can play a role in telomere maintenance, although it does not directly bind with it but rather interacts through TRF2 and possibly participates in T-loop formation (Saldanha et al., 2003). Among these single-stranded binding proteins is found POT1; this binds to a telomeric salient with exceptionally high specificity. It adopts an oligosaccharide-oligonucleotide (OB) joining fold with two forks that overhang to form a clamp for binding to DNA (Lei et al., 2003). When the PTO1 binding domain is mutated, there is no telomeric end fusion, but rather an increase in telomere extension by the telomerase; thus, one of its functions is to block the access of this enzyme to the DNA. TRF1 interacts with POT1; thus, it is the length control terminal transductor for TRF1. The more TRF1, more POT1, which leads to an increase in telomerase inhibition (Mattern et al., 2004). POT1 is necessary to maintain structure in telomere salients, protecting the cell against apoptosis, avoiding chromosomal instability and senescence, and interacting with TRF2 at the T-loop formation point, with which it cooperates for maintaining telomere integrity (Yan et al., 2005).

Recently, it was discovered that Rap1 is an important factor for avoiding telomere recombination and fragility (Martínez & Blasco, 2011).

10. The telomerase

Telomerase is a Ribonucleoprotein (RNP) composed of two units: the catalytic subunit, TERT, and a RNA template, TERC. TERT is a member of the family of reverse transcriptases related with non-LTR retrotransposons and group II introns. Its reverse transcriptase domain is found at the middle of the carboxyl-terminus and it supplies the active site for catalysis (Cech, 2004). TERC, also called TR, is highly expressed in all tissues, it not being important whether they possess telomerase activity or not, and it contains a short sequence that acts as a template from which DNA repeats are copied (Cong et al., 2002). Telomerase carries its own template and is restricted to copying solely a small segment of its RNA. Thus, implicit in telomerase polymerization activity is its ability to specify the template region and its limits, and also a mechanism for maintaining itself as a stable RNP while carrying out synthesis, because it allows the template to move through the active site during the synthesis process of a repeat, to later translocate itself and initiate the synthesis of another repeat. (O'Reilly et al., 1999; Cech, 2004).

When the telomere catalytic subunit in mouse mutates, the first generation that lacks telomerase activity is phenotypically normal, with long telomeres. After four to six generations, its telomeres become very short, and the mice suffer from infertility, proliferation defects, and the risk of apoptosis in organs that undergo constant turnover, which diminishes their life span, while a *TERC* gene mutation causes Dyskeratosis congenita (DKC), a disease in which, among other characteristics, the telomeres are abnormally short (Blasco, 2005).

There are accessory factors that aid the telomerase in acting on the telomere, such as dyskerin and TP1. Dyskerin is important for ribosomal processing because it binds to many small nucleolar RNA, and it is implicit in TERC and even TERT processing or stability because its small nucleolar RNP domain reached maturation in the nucleolus and later binds to the dyskerin (Cech, 2004). TP1 can form one or more structures that mediate interactions with other telomerase- or telomere-binding proteins such as TRF. The TP1 pattern of expression is not restricted to tissues and cell lines that express telomerase activity; therefore, it is not an essential subunit (Harrington et al., 1997).

Chai et al. (2006) found that it is possible that telomerase preferentially extends the leader chain of 20-30 nucleotides per replication round in order to produce a salient similar to that of the delayed chain, because the leader-chain salient is smaller, which otherwise would affect the conformation of telomere structure.

Telomerase-to-telomere access regulation is carried out by telomere-associated proteins, for example, TRF1 and TRF2; on forming the T-loop, these inhibit telomerase binding, while POT1 binding to the salient does not permit coupling of the enzyme so that this would extend it.

Mutations in telomerase components produce premature dysfunctions in adult stem cells and reduce longevity (Mitchell et al., 1999).

11. Telomere position effect (TPE)

At present, it is accepted that telomere clipping can affect gene expression in subtelomeric regions, which can lead to modification of the Biology of the cell prior to initiation of replicative senescence (Baur et al., 2001).

The Position variegation effect (PVE) refers to inactivation of a gene, which occurs when it is removed from its normal context by means of a rearrangement or by transgene insertion. The best known example of this is the result of the expression of the euchromatic white gene in Drosophila, which is responsible for the red color of the eye. Provoked by a rearrangement in chromosome X that causes its relocation near the heterochromatin region, it eliminates function in some cells, which produces mottled pigmentation. The explanation for silencing of the white gene in some cells and not in others is that condensed and inactive conformation of pericentric heterochromatin is dispersed on the rearrangement break and randomly inactivates nearby genes (Henikoff, 1990). This chromosomal position effect affects up to a distance of approximately 1Mb and reflects a genetic inactivation gradient that is inversely correlated with distance (Wakimoto, 1998). The PVE phenomenon suggests that heterochromatin forms a transcriptionally repressor environment within which the presence of heterochromatically active resident genes is somewhat paradoxical, because these genes exhibit reciprocal heterochromatic PVE, that is, a heterochromatic gene will undergo variation if it is translocated to an euchromatic ambit. From this arises the suggestion that these genes have developed transcriptional dependence in factors that normally silence the expression of other genes (Schulze et al., 2005). Among proteins known to possess an important function in gene silencing in Drosophila is found HP1, which is a protein associated with pericentric heterochromatin. It has unequal distribution through the genome and is principally associated with the fourth chromosome. Specifically, it exerts an impact on structural organization and does not only cover the DNA or serves to direct all repetitive DNA sequences toward the repressive structure (Cryderman et al., 1999).

In the case of *Saccharomyces cerevisiae*, the heterochromatin is not cytologically visible; however, it presents position effects in three places: the telomeres; the rDNA locus, and the silent "mating-type" loci (HML and HMR). When a gene is found in one of these sites, its transcription is repressed. As in PVE, silencing depends on gene localization and not on its sequence (Chen & Widom, 2004). Several proteins are involved in the repressive chromatin, including H3 and H4 histones, their acetylases and associated deacetylases, the molecular regulators Sir1-Sir4, and the Origin recognition complex (ORC) (Pryde & Louis, 1999). The four Sir proteins are necessary for transcriptional silencing in HML and HMR, while only Sir2p, Sir3p, and Sir4p are required for telomere silencing and only Sir2p is required for rDNA silencing (Chen & Widom, 2004). TPE was described for the first time in 1990 through generation of a terminal deletion that caused the *URA3* gene (the gene necessary for uracil synthesis) to be localized 6 kb from a telomere. This new gene position provoked its transcriptional repression, which was lost when this was localized 20 kb from the telomere (Gottschling et al., 1990).

It was in 1992 that Wright and Shay set forth the possibility that TPE exists in humans. However, the first experimental proposal to identify TPE in humans, carried out by Bayne et al. (1994), did not yield positive results because changes were not found in the hygromycin-resistant gene on generating deletions in the long arm of chromosome X. Again, this time in

1996, Sprung et al. (1996) sought to study the telomere-length effect on HSV-tk promotor expression, utilizing the KB319 cell line (SV40-transformed fibroblasts); the authors integrated a plasmid with the neo-gene at the end of chromosome 13 and found no effect on neo-gene expression when telomere length ranged from 25-0.5 kb; this leads them to suggest that chromatin structural differences conferred by telomere length do not affect the expression of nearby genes. A 130-kb microdeletion in the end of chromosome 22q in cells from a child with mental retardation; the broken end had been repaired by telomere addition, and consequently a unique DNA region that was normally localized at a distance of >100 kb from the telomere was now adjacent to it. This was the model employed by Ofir et al. in 1999 to demonstrate that telomeric sequences influence the activation of nearby replication origins, delaying the synchronization of replication at mid-S phase. The latter suggests that if human telomere repeats silence genes adjacent to repaired ends, then it is also conceivable that nearby genes may be epigenetically inactivated. On the other hand, Kilburn et al. (2001) found that the presence of a telomere sequence in an *APRT* gene intron in hamster ovary cells only had a modest effect on its expression. Finally, it was Baur et al. in 2001 who, employing a luciferase reporter, supplied convincing evidence of transcriptional silencing near telomeres in humans. The authors found that on placing the reporter adjacent to telomere repeats, there was 10-times lower expression than when they placed it at non-telomeric sites. However, the authors also found that TPE in humans required a histone deacetylase, because on treating the telomeric clones with trichostatin A (a histone deacetylase inhibitor), luciferase expression was restored. Koering et al. (2002) obtained similar results utilizing the *EGFP* reporter gene in C33-A cells (undifferentiated cervical carcinoma), reverting the repressor effect on employing trichostatin A, and they suggested that the position effect depends on the organization of telomeric chromatin, due to that they encountered the release of heterochromatin proteins HP1α and HP1β. Pedram et al. (2006) developed embryonic stem cell clones of mouse with unique-copy gene markers and found that telomeric transgenes were not silenced in cells obtained from 3-day-old embryos as a result of their demethylation during early development, which led the authors to suggest that TPE also plays a role in embryo development. On the other hand, Wright and Shay (1992) also propose that progressive changes in presenescent cells can be the result of the reorganization of telomere chromatin and of the corresponding silencing or desilencing of subtelomere genes. This hypothesis has been extended to include the possibility that silenced proteins can be released from telomeres when the latter are shortened, in order to affect the expression of genes at internal non-telomere sites (Wood and Sinclair, 2002). This idea was based on studies with *S. cerevisiae*, in which it was demonstrated that gene markers inserted <4 kb from telomere repeats are frequently repressed and replicated at the end of the S phase (Dubrana et al., 2001). Although the loss of TPE is not the senescence trigger, it can be responsible for progressive changes in gene expression as a function of replicative age (Wood and Sinclair, 2002).

12. Role of telomere length in subtelomeric gene expression and its possible relation to cellular senescence

To date, there is only one report to our knowledge that studies *in vivo* TPE in human subtelomere genes. The results obtained suggest that the expression of these genes can be influenced by alterations in local heterochromatin structure so that this obstructs access to transcriptional factors (Ning et al., 2003). Due to the fact that few evidence exist about of

how age-related telomere length affects the expression of specific human subtelomeric genes, we analyzed the relationship between telomere length and gene expression levels in fibroblasts derived from human donors at ages ranging from 0-70 years. We studied three groups of genes localized 100-150 kb, 200-250 kb, and >300kb away from telomeres. We found that chromatin modifier-encoding genes *Eu-HMTase1*, *ZMYND11*, and *RASA3* were over expressed in adults and implicated in chromatin restructuring (Hernández-Caballero et al., 2009). These genes are interesting because can participate in cellular senescence through the p53-p21Cip1 pathway and can also participate in chromatin restructuring, interacting with remodeling factors including ATP-dependent helicases, histone deacetylases, and histone methyltransferases (Velasco et al., 2006; Zhang et al., 2007). On the other hand, *Eu-HMTase1* can regulate H3-K9 mono- and dimethylation in euchromatin (Tachibana et al., 2005).

13. Conclusions

Undoubtedly the Antagonistic pleiotropy helped to understand the seemingly contradictory functions of the cellular senescence, nevertheless still it is not clear how does the senescence response balance tumour suppression, tissue regeneration and ageing phenotypes, for which it will be needed of a major number of studies.

Our results suggest that the expression of the subtelomeric genes modifies with the age, probably as result of decrease of the telomere length. How the changes on telomere length affected the expression of subtelomeric genes? Recently Martínez et al (2010) demonstrated that the RAP1 protein associated with the telomere, also it associates to the subtelomeric genes. Probably this protein might be involved in TPE.

The Senescence is a complex phenomenon where different factors are involved, the changes in expression of subtelomeric genes, as result of the age, is another variable that will help to the understanding cellular senescence.

14. Acknowledgment

15. References

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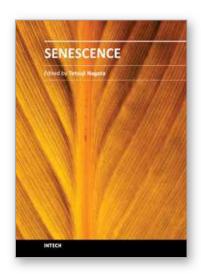
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Senescence

Edited by Dr. Tetsuji Nagata

The book "Senescence" is aimed to describe all the phenomena related to aging and senescence of all forms of life on Earth, i.e. plants, animals and the human beings. The book contains 36 carefully reviewed chapters written by different authors, aiming to describe the aging and senescent changes of living creatures, i.e. plants and animals.

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