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Telomeres and Reproductive Aging

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1. Introduction

Telomeres are special deoxyribonucleic acid (DNA) structures that "cap" the ends of eukaryote chromosomes. The term telomere derives from the Greek words telos, meaning "end", and meros meaning "part". The existence of these end-parts of chromosomes was first suggested in 1938 by Muller (Muller, 1938). Telomere length is involved in biological aging and disease processes. Telomere length is affected by several factors, such as aging, aging related diseases, gender, genetic and environmental factors. Telomere length, which is a highly variable and heritable trait (Jeanclos et al., 2000; Slagboom et al., 1994; Nawrot et al., 2004; Vasa-Nicotera et al., 2005; Andrew et al., 2006; Biscoff et al., 2005), is greater in women than men (Jeanclos et al., 2000, Nawrot et al., 2004; Vasa-Nicotera et al., 2005; Biscoff et al., 2005, Benetos et al., 2001; Mayer et al., 2006; Fitzpatrick et al., 2007). As well as genetic factors environmental factors are also influential on leukocyte telomere dynamics. Environmental factors, including smoking (Nawrot et al., 2004; Valdes et al., 2005), obesity (Fitzpatrick et al., 2007; Valdes et al., 2005; Gardner et al., 2005), psychological stress (Epel et al., 2005) and low socio-economic status (Cherkas et al., 2006) are associated with shortened leukocyte telomere length. Leukocyte telomere length can be determined relatively easily and the processing of leukocytes is rather simple. Leukocyte telomere length has been studied extensively in humans in relation to both the aging process and several pathologies. There are many correlative studies demonstrating a link between telomere length and aging (Slagboom et al, 1994, Wu et al, 2003).

Aging has been defined as a normal biological process, which involves the cumulative deposition of damaged and defective cellular components, loss of cell or organ physiological functions and inability to perform physical activity. Cellular senescence and aging have been reported to be related to shortening telomere length (Aubert & Lansdorp, 2008). Multiple surveys conducted in human populations have demonstrated the shortening of telomere length in various tissues during the aging process. Many theories have been proposed for aging, yet still, no single theory is able to account for all the different views. Among the most widely accepted theories on aging are the Hayflic limit theory and telomere theory (Gavrilov & Gavrilova, 2003). Shortened leukocyte telomere length is observed in individuals with aging-related diseases, including hypertension (Jeanclos et al., 2000; Benetos et al., 2001), insulin resistance (Gardner et al., 2005; Demissie et al., 2006; Aviv et al., 2006), atherosclerosis (Brouilette et al., 2003; Benetos et al., 2004), myocardial infarction (Brouilette et al., 2003, 2007; Cawthon et al., 2003), stroke (Fitzpatrick et al., 2007) and

dementia (von Zglinicki et al., 2000; Panossian et al., 2003). Furthermore, it is suggested that the relationship between leukocyte telomere length and some of these variables could be modified by the aging process itself (Aviv et al., 2006). Unlike other systems, first signs of reproductive aging begin at mid 30 in normal condition. Telomere may be one of the responsible factors in also reproductive aging especially in women.

2. Telomere biology

The nucleoprotein complexes, referred to as telomeres, are specialized structures located at both ends of linear eukaryote chromosomes. Human telomeres are composed of a short repetitive DNA sequence (TTAGGG) and bound by a six-protein complex known as shelterin. TTAGGG repeat-binding factors (TRF) 1 and 2, bind to the TTAGGG sequences in double-stranded DNA, and one subunit, proteins for the protection of telomeres (POT1), bind to these sequences in single stranded form (de Lange, 2005; Pan et al., 2011). They are linked by three additional shelterin proteins, TIN2, TPP1, and Rap1, composing a complex called shelterin that enables cells to distinguish telomeres from sites of DNA damage (Fig.1). Three shelterin subunits, TRF1, TRF2, and POT1 directly recognize TTAGGG repeats. TRF1 and TIN2 regulate telomere length, TRF2 prevents end to end fusion and activation of DNA damage response. It has been reported that, additional proteins capable of interacting with telomeric proteins which are involved in DNA damage response and double-strand break repair also have implications for telomere length regulation and chromosome end protection (De Boeck et al., 2009; Gilson and Geli, 2007; Palm and de Lange, 2008).
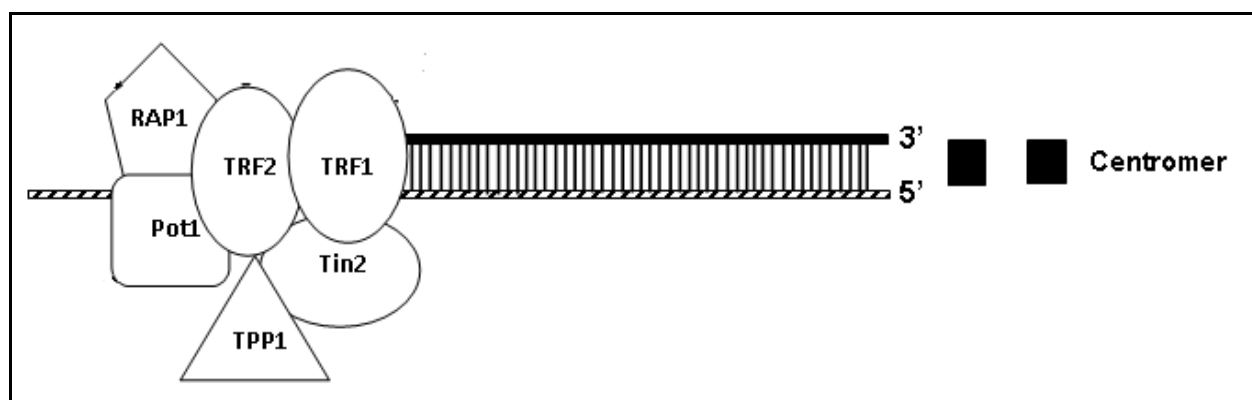

Fig. 1. **Schematic representation of chromosome termini. In mammals** telomeric sequences are enclosed by a complex which is composed of 6 different proteins **(TRF1, TRF2, POT1, TIN2, TPP1 AND RAP1)** that have specificity for either the single or double stranded DNA, **called shelterin**.

Telomeres act as the cap of the chromosome and maintain genomic integrity by preventing end-to-end fusions. (Murnane & Sabatier, 2004). Telomeres shorten with age through at least two mechanisms: (*1*) replicative senescence in dividing cells (*2*) and a damage response to reactive oxygen in non-dividing cells (Passos & von Zglinicki, 2005).

The shortening of telomeres occurs in each round of cell division consequential to the inability of conventional DNA polymerases to replicate the ends of linear chromosomes, in other words, as a result of the so-called 'end replication problem'. DNA replication involves

the simultaneous copying of antiparallel DNA strands, such that replication proceeds in opposite directions, along a "leading" strand and a "lagging" strand. Daughter strand DNA synthesis takes place progressively on the leading template in the 5' to 3' direction, whilst on the lagging strand template, although seemingly backward in the form of Okazaki fragments, DNA synthesis also proceeds in the 5' to 3' direction. The leading daughter strand is almost completely synthesized, by the time the DNA polymerase reaches the 5' end of the leading template. However, a primer is required to start replication. If the RNA primer occupying the 5' end of the daughter strand is removed, it is not possible for the overlapping single strand to be replicated. The localization of this primer is the beginning of the leading strand and the end of the lagging strand. Consequently, the 5' end of each of the antiparallel daughter strands becomes one primer-length shorter. Chromosomes grow shorter with each consecutive replication (Fig 2).
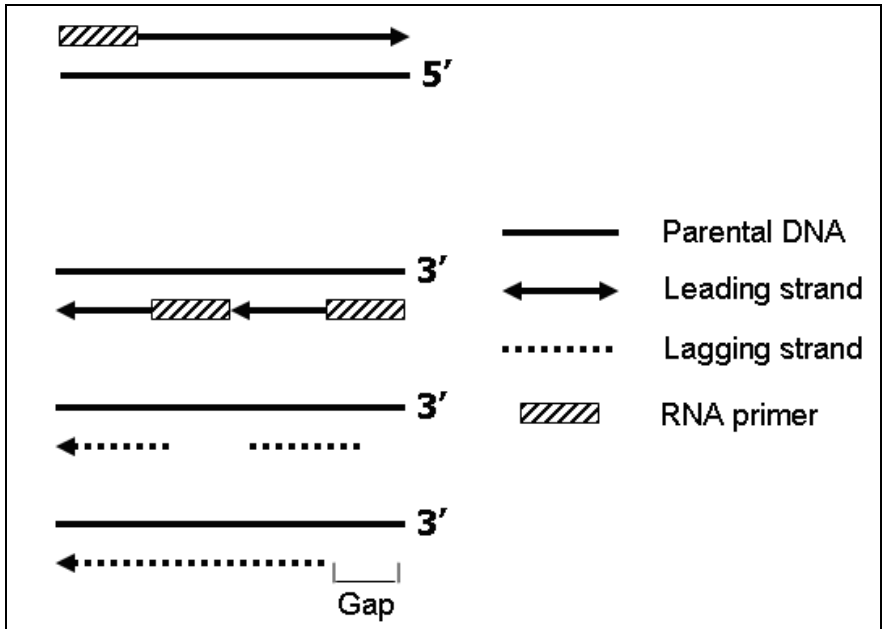

Fig. 2. In a linear chromosome, the leading strand can be synthesized by DNA polymerase until the end of the chromosome. On the other hand, in the lagging strand, synthesis by DNA polymerase is based on a series of fragments, referred to as Okazaki fragments, each of which requires an RNA primer. When the RNA primer occupying the 5' end of the daughter strand is removed, it is not possible for the overlapping single strand to be replicated. The localization of this primer is the beginning of the leading strand and the end of the lagging strand. Consequently, the 5' end of each of the antiparallel daughter strands becomes one primer-length shorter. Chromosomes grow shorter with each consecutive replication.

Due to the end replication problem, it is estimated that, in most human cells, a loss of less than 10 base pairs occurs per division. In fact, most often, the rate of loss is much higher, calculated as 50–200 base pairs per division in humans (Takai et al., 2003). The underlying reason of this difference has aroused great interest, but remains poorly understood (Lansdorp, 2005). Oxidative stress is thought to be one of the main factors involved (Houben et al., 2008). Exonuclease activity degrading the 5' end is another major factor. The

degradation of the primer on the lagging strand and the action of a putative 5' to 3' exonuclease lead to shortening of the 5' end of the telomere and the formation of a 3'-end overhang structure (Wai, 2004). Both, the nuclease-dependent resection of telomeres create single-stranded G-rich-strand overhangs and the inability of DNA polymerase to copy through the ends in lagging-strand during DNA replication cause to loss of telomeric repeats in each replication (Shay & Wright, 2000). Telomeric DNA is much more susceptible to oxidative damage than nontelomeric DNA, at least partly due to its high guanine content. While most studies investigating the effects of oxidative stress on telomere loss have been conducted in vitro (Richter & von Zglinicki, 2007), correlative and experimental studies have begun to demonstrate the link between oxidative stress and the rate of telomere loss in vivo (Houben et al., 2008; Cattan et al., 2008). Telomeres shorten throughout the lifespan of human cells. When telomeres shorten to a critical length, the cell ceases mitotic division, thus, replicative senescence occurs. This phenomenon, which is referred to as the Hayflick limit (Hayflick & Moorhead, 1961), demonstrates that telomere length acts as a major determinant of replicative capacity. Therefore, it is indicated that, telomere length, in a way, serves as a mitotic clock and constitutes a marker of biological aging, representative of the aging process other than chronological aging (the measure of time elapsed since a person' birth). In his research dating back to 1961, Hayflick showed that a cell culture population of normal human fetal cells divided between 40 and 60 times. Accordingly, he suggested that cells were capable of undergoing only a limited number of cell divisions before entering a senescence phase (Hayflick & Moorhead, 1961). Because of limited telomerase activity in normal somatic cells, it is presumed that, at the Hayflick limit (Ml), one or more telomeres lose TTAGGG beyond a crtical threshold activating a checkpoint mechanism that arrest cell growth. If partially transformed cells that skip this checkpoint without telomerase being activated, they continuously lose telomeres until "crisis" (M2). Cells capable of activating telomerase, most probably by mutation, as seen in most of cancer cells could survive the crisis. Only then can telomeres be maintained at stable length (Fig 3).

Senescent cells may produce protein aggregates different than those pertaining to quiescent but non-senescent adjacent cells. The homeostasis of tissues characterized by the senescence of cells, which emerges and is recognized as aging, could be changed (Shay & Wright, 2007). The shortening of telomeres is encountered in rapidly proliferating cells of the skin, gastrointestinal system and blood.

An oxidation-trigerred DNA damage response that excises the oxidized sequence leads to telomere attrition also exist in non-dividing cells (Passos & von Zglinicki, 2005). ROS-induced telomere shortening may result from direct injury to guanine repeat telomere DNA by ROS. A large number of independent studies have shown that (von Zglinicki, 2002; Serra et al., 2003) telomere shortening increased significantly under mild oxidative stress, in comparison to that observed under normal conditions. In somatic cells, the rate of telomere shortening can be suppressed by the addition of an antioxidant. Furumoto et al showed that the telomere shortening rate slowed after enrichment with ascorbic acid, which is a strong antioxidant (Furumoto et al., 1998). In most cases, the contribution of oxidative damage to telomere loss is much greater than that of the end-replication problem alone. Telomeres, as triple-G-containing structures, are highly sensitive to damage by oxidative stress (Henle et

al., 1999), alkylation (Petersen et al., 1998) or ultraviolet (UV) irradiation (Oikawa et al., 200)]. Thus, stresses of high intensity may lead to telomere shortening without DNA replication, as a result of the induction of telomeric double-strand breaks at high frequency (Bar-Or et al., 2001; Oikawa et al., 2001).
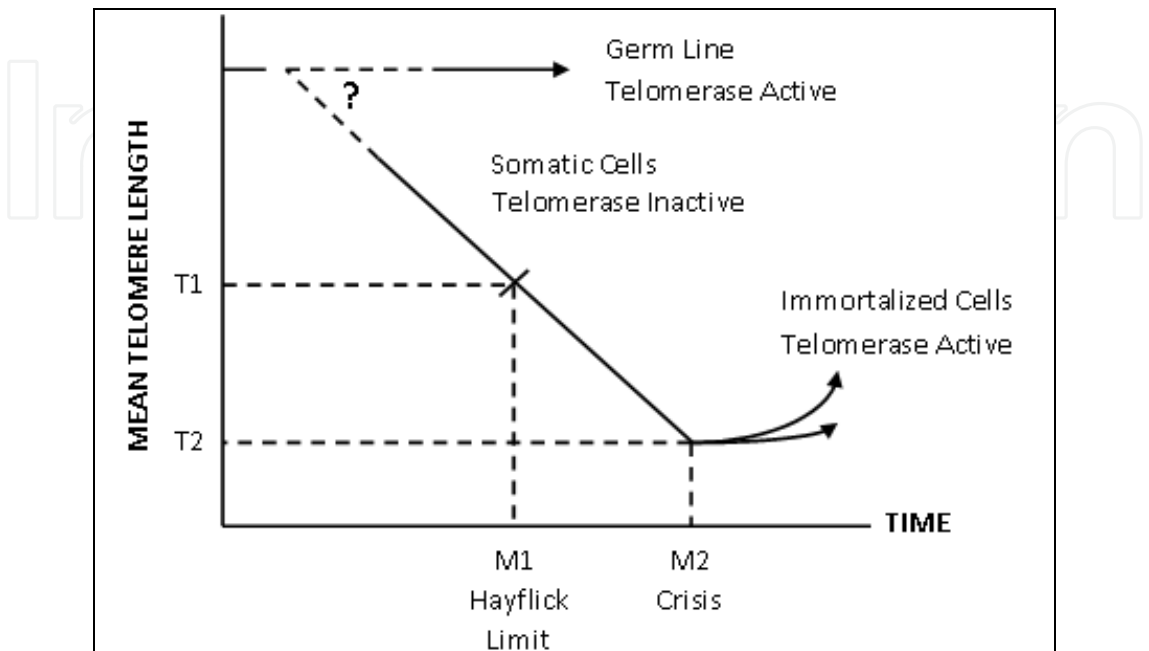

Fig. 3. **Schematic representation of the telomere hypothesis of cell aging and immortalization.** Alterations observed in telomere length over time (in cell divisions) are shown for germ line, normal somatic and transformed cells. Events in the early embryonic stage, at the beginning of the time axis, remain unknown (dotted lines). As telomere length is maintained in germ-line cells, it is thought that telomerase is activated at some point in gametogenesis, yet it is unclear whether telomerase activity is present in the early embryo prior to germ-line development. On the contrary, the decrease observed in telomere length and the lack of telomerase activity in normal somatic cells, suggest that telomerase is repressed in these cells. It is presumed that, at the Hayflick limit (Ml), one or more telomeres lose a threshold amount of TTAGGG, pointing out to a checkpoint in cell growth. The mean telomere length at this point is shown as T1. Partially transformed cells that skip this checkpoint without telomerase being activated, continuously lose telomeres until "crisis" (M2), at the point where most cells have critically short telomeres on many chromosomes (mean telomere length = T2). Cells capable of activating telomerase, most probably by mutation, could survive the crisis. Only then can telomeres be maintained at stable length.

The telomere end replication problem is solved by the use of a cellular enzyme called telomerase. Telomerase is a ribonucleoprotein complex composed of a catalytic subunit of component telomerase reverse transcriptase (TERT) responsible for the synthesis of new telomeric DNA repeats, and a telomerase RNA component (TERC) that functions as a template (Aubert & Lansdorp, 2008). This enzyme is capable of compensating for progressive telomere attrition through the de novo addition of TTAGGG repeats to chromosome ends (Greider & Blackburn, 1985) as well as of preventing telomere shortening

in some cells, including male germ, stem and cancer cells (Keefe & Liu, 2009). The accelerated aging phenotype occurs in both TERC and TERT gene knockout mice (Greer & Brunet, 2008). As well as various pathologies, telomere dysfunction in late generations also leads to decline in fertility in female mice, eventually resulting in sterility (Lee et al., 1998; Herrera et al., 1999). Recent studies have revealed that telomerase function is regulated by an epigenetic mechanism involving histone methylation and deacetylation as well as CpG methylation. Strikingly extended telomeres were detected in mouse embryonic stem cells with deficient DNA methyltransferase (DNMT)1, or both DNMT3a and DNMT3b (Gonzalo et al., 2006). Increased telomere length is observed in histone methyltransferase-deficient MEFs. Elimination of acetylated histone H4 lysine 12 (H4K12) at telomeric heterochromatin resulted in reduction of telomere replication and recombination (Zhou et al., 2011).

Meiocytes may display telomerase independent mechanisms for telomere elongation that are based on homologous recombination between telomeres of different chromosomes. In other words, these cells may present with an alternative pathway for the lengthening of telomeres (ALT) (Chin et al., 1999). A high degree of heterogeneity of telomeres, including among others elongated and shortened telomeres, is generated by the ALT pathway in somatic cells with ALT activity (Nittis et al., 2008). However, to date, the presence of this mechanism in germ cells has not been proven.

Leukocyte telomere length varies greatly among individuals and shortens with aging. Significant variations are observed, in particular, during the first few years of life (Rufer et al., 1999). Telomere length remains relatively stable throughout childhood, preadolescence and adolescence. Eventually, telomere length attrition reaches its peak at very old age, beyond 100.

3. Reproductive aging

3.1 In males

Spermatogenesis and male reproductive functions gradually decline with aging. Semen quality and pregnancy outcomes appear to decline. Dunson et al showed that semen parameters begin to decline after 35 years of age. As a result, male fertility also decreases substantially in the late 30s and continues to decrease after the age of 40 (Dunson et al., 2004).

In a study on couples undergoing intracytoplasmic sperm injection (ICSI), it was found that increased age in men with oligozoospermia resulted in decreased implantation and pregnancy rates. In these couples, pregnancy rates decreased 5% for each year of paternal age, however, this effect was not observed in normozoospermic men (Ferreira et al., 2010). Levels of ROS that bind to the DNA that may cause DNA fragmentation have been found to be significantly higher in seminal ejaculates of healthy fertile men older than 40 years. Protective antioxidant scavenging enzyme concentrations are low in spermatozoa, which may reduce the chances of pregnancy, as men become progressively less fertile with age (Desai et al., 2010; Cocuzza et al., 2008). Based on findings detected in infertile men, it has been shown that aging affects the chromatin integrity of spermatozoa (Vagnini et al., 2007; Plastira et al., 2007). Numerical (such as disomy of chromosome 3, higher incidence of extra group C chromosomes including X chromosome, and group G chromosome or by extra

group D and F chromosome) (Sartorelli et al., 2001) and structural aberrations in sperm chromosome also increase with paternal age. When a female baby is born, mitotic divisions of primordial germ cells have already been completed and meiosis has been arrested at prophase I. Therefore, a female baby is born with all the eggs she will have throughout her life, whilst mitotic spermatogenesis is an ongoing process throughout most of the male's life. The number of germ-line divisions is much higher in males than females. Consequently, more replications enhance the chance for spontaneous germ-line mutations that arise during the mitotic phase of spermatogenesis (Crow, 2000; Glaser & Jabs, 2004; Tarin et al. 1998; Kuhnert & Nieschlag, 2004). Transmitted to their offspring by older fathers, these germline mutations might cause an increased rate of clinical disorders such as autism, schizophrenia, and autosomal dominant disorders including achrondroplasia, osteogenesis imperfecta, and Marfan syndrome. As well as numerical and structural aberrations in sperm chromosome, some clinical manifestations such as cryptorchidism, hypospadias, and testicular cancer also increase with paternal age (Stewart & Kim, 2011). Fisch et al found that a paternal effect on the increased risk of Down syndrome was an important factor when both parents were over 35, but not when the female partner was younger than 35 years of age. In this study, the incidence of Down syndrome seemed to be related to paternal age at an approximate rate of 50% when the male was older than 35 and the female was older than 40 (Fisch et al., 2003).

Two previous studies conducted in 125 (Unryn et al., 2005) and 2,433 (De Meyer et al., 2007) participants demonstrated that leukocyte telomere length in adult offspring and paternal age were positively correlated with each other. This could be explained by the presence of a subset of sperm with longer telomeres in older men. It is possible that numerous replications of the male germ-line that occur with advancing age exert a powerful selection pressure that produces stem cells resistant against the effects of aging (Wallenfang et al., 2006). Sperm with greater telomere length might emerge from a subset of germ-line stem cells less resistant to aging-related oxidative stress, either due to increased resistance to its action—or having undergone fewer replications before meiosis. Epigenetic processes that occur in germ-line stem cells with advancing age in men may result in the elongation of telomeres (Blasco, 2007). Through the inheritance of the particular genetic constitution of such sperm (with or without DNA mutations) across generations, some offspring with longer leukocyte telomere length would emerge.

Although available data stress the important impact of male aging on telomere status, further studies are needed to clarify such correlation.

3.2 In females

During the aging process, in addition to several physiological changes in other systems, age-related changes, including the decline of ovarian functions resulting from reductions in the quantity and quality of the oocyte/follicle pool, also occur. Two important changes are observed in human ovaries with aging: 1) decline in oocyte genomic stability leading to aneuploidy (Hassold & Hunt, 2001) and 2) depletion of ovarian follicles (Faddy et al., 1992; Faddy, 2000).

Women display a marked increase in infertility, chromosomal nondisjunction associated miscarriage, and birth defects, as a result of reproductive aging characterized by a markedly

increased duration of meiotic dysfunction. In women, fertility begins to decline starting from the mid-30s. Furthermore, as women grow older, the rate of miscarriage and/or aneuploid offspring increases dramatically. In clinically diagnosed pregnancies, trisomy incidence tends to be low (2-3%) in women in their 20's, yet rises to about 35% in women in their 40's (Hassold & Hunt, 2001). Previously conducted studies on *in vitro* fertilization (IVF) have proven that female age constitutes the most significant factor influential on clinical outcome (Wright et al., 2006). Based on studies investigating the effects of aging on oocytes, it has been concluded that maternal age has negative effect on the expression of oocyte genes responsible for major cellular activities such as cell cycle regulation, energy pathways and mitochondrial functions, and oxidative stress (Hamatani et al., 2004, Steuerwald et al., 2007).

3.2.1 Decline in oocyte genomic stability leading to aneuploidy

Most human aneuploidies occurring in embryos originate from the egg and not sperm (May et al., 1990; Hassold et al., 1987, 1991; Takaesu et al., 1990; Martin & Rademaker, 1987). Indirect proof suggests that, in addition to the reduction of oocyte quantity, impaired oocyte quality also contributes significantly to the age-related decline of fertility in women (Ottolenghi et al., 2004). As women age, their oocytes increasingly show abnormalities in chromosome segretion and spindle morphology. Keefe and co workers proposed a telomere theory of reproductive aging in women (Keefe et al., 2006). According to this theory, telomere dysfunction in oocytes is responsible for several reproductive changes including meiotic dysfunction, increased aneuploidy resulting in miscarriage, decreased fertility rate and birth defects. In older women, the prolonged exit of oocytes from the production line and their chronic exposure to reactive oxygen results in the shortening of telomeres. In return, the shortening of telomeres brings about a reduction in chiasmata, the presence of abnormal meiotic spindles in oocytes, as well as cell cycle arrest, apoptosis and cytogenetic abnormalities in resulting embryos (Keefe et al., 2006).

3.2.1.1 Oocyte senescence

In females, meiosis begins during fetal development, becomes arrested at prophase I before birth, and remains in this stage until prior to ovulation in adulthood, up to 50 years later in humans, by means of the synthesis of several RNAs and proteins. At that time, oocytes with a diameter of 15–20 μm develop to become fully grown oocytes of 70–150 μm (Bacharova, 1985). Based on observations in the mouse model, it has been suggested that aging impairs the accumulation of maternal RNAs either required for oocyte-specific processes and metabolism, or presumably stored for later use during early embryonic development prior to activation of the embryonic genome (Hamatani et al., 2004). The long interval between meiotic prophase I arrest in the fetus and each ovulation cycle in aged women increases the incidence of aneuploidy.

3.2.1.1.1 Meiotic chromosome and telomere

The aging oocyte is responsible for problems associated with maternal age (Sauer, 1998; Stolwijk et al., 1997). As they are involved in the tethering of chromosomes and the

facilitation of their alignment, pairing and synapsis, as well as the formation of chiasmata during early meiosis, telomeres play a major role in meiotic reproduction (Scherthan et al., 1996; Scherthan, 2006; Roig et al., 2004; Bass et al., 1997). The mechanisms of meiotic telomere maintenance and dynamics, including attachment to the nuclear envelope, are only partially understood (Adelfalk et al., 2009). In the early stage of meiosis, in order to facilitate the homologue alignment required for the formation of chiasmata, telomeres aggregate around the nuclear envelope, forming 'bouquets' with a stalklike attachment to the nuclear envelope. This structure aids in the formation of the meiotic spindle and is therefore critical to chromosomal division. In oocytes, the main cause of telomere shortening is reactive oxygen species (Liu et al., 2002a), which increase with maternal aging. Experimental telomere shortening by several generations in the telomerase-null state (Liu et al., 2002b), or exposure to pharmacologically induced reactive oxygen in mice, results in impaired chiasmata and synapsis, and even abnormal spindles and chromosome misalignment (Liu et al, 2002b; Liu et al., 2004). Furthermore, females present with chromosome misalignment, lack of efficient metaphase checkpoint control during meiosis, progression from the MI stage to the MII stage (LeMaire-Adkins et al., 1997; Roeder, 1997). Structural abnormalities in the meiotic spindle, including asymmetry of the spindle poles and failure of chromosomes to align on the metaphase plate, are present in almost 80% of eggs aspirated from women over the age of 40, compared to only 17% of eggs from younger controls (Keefe et al., 2007). The mechanisms underlying chromosome misalignment and disruption of meiotic spindles caused by telomere dysfunction are not well understood. In a study conducted by Wood et al, female Mlh 1 mutant mice, which lacked normal recombination, also exhibited abnormal spindle assembly (Woods et al., 1999), and this may have caused improper homologous chromosome pairing and recombination during early meiosis. But still there is no clear information on whether telomeres play a role in spindle organization and chromosome segregetion in meiosis (Liu et al., 2002a). Experimental studies in adult mice have demonstrated that checkpoints for meiotic chromosome behaviour during the metaphase-to-anaphase transition are more efficient in males compared to females (Hunt et al., 1995; Le-Maire Adkins et al., 1997)]. Making use of telomerase null mice, it was investigated whether telomerase deficiency and/or telomere shortening could influence meiotic progression. The meiotic resumption and division (maturation) of germinal vesicle oocytes from fourth-generation telomerase null mice and first-generation telomerase null mice, as well as wild-type controls were compared. Chromosome misalignment and disruption of meiotic spindles at the metaphase stage appeared frequently in oocytes from fourth-generation telomerase null mice with very short telomeres, while meiotic progression, chromosome behavior, and spindle morphology in first-generation telomerase null mouse oocytes were comparable to those of wild-type mouse oocytes (Liu et al., 2002b).

In mammalian oogenesis, the sister chromatid cohesion is mediated by the multi-subunit protein complex called cohesin, which is composed of the meiosis-specific subunits REC8, STAGE3, SMC1β, and SMC3 (Garcia-Cruz et al., 2010; Prieto et al., 2004; Revenkova & Jessberger, 2005). It has been proposed that chromosome missegregation and aneuploidy in aged oocytes could result from loss of sister chromatid cohesion (SCC) through slow deterioration of cohesin (Hassold & Hunt, 2001; Hunt & Hassold 2008; Hodges et al., 2005). The cohesin component SMC1β prevents oocyte telomere shortening in mice (Adelfalk et al., 2009). It was observed that, in the oocytes of aged senescence-accelerated mice (SAM), meiotic cohesin proteins including REC8 (recombinant 8), STAG3 (stromal antigen 3) and

SMC1 β that are located between sister chromatids were significantly reduced. In the study of Adelfalk et al., it was reported that, cohesion SMC1β which was reduced significantly in aging, is necessary to prevent telomere shortening, and SMC3, present in all known cohesion complexes, properly localizes to telomeres only if SMC1β is present (Adelfalk et al., 2009). Therefore it is one of the responsible factors, aging related telomere shortening in oocyte and meiotic-dysfunction in female. Furthermore, cohesion degradation was more pronounced in SAM compared to hybrid F1 mice with age, which may explain the vulnerability of SAM to aneuploidy. This ageing mouse model revealed that defective cohesin is associated with increased incidence of chromosome misalignment and precocious segregation (Liu & Keefe, 2008). In a study conducted by Hodges et al, the aging of female SMC1 β −/− mice was associated with a dramatic loss of chiasmata. In parallel with the aging of SMC1 β −/− oocytes, the loss of sister chromatid cohesion in metaphase I oocytes increases significantly (Hodges et al., 2005). This supports the increasingly distal localization of chiasmata on metaphase chromosomes, indicative of the inability of chiasmata being prevented from moving and slipping off chromosomes without SMC1β mediated sister chromatid cohesion (SCC). The expression of SMC1β cohesin takes place during prophase I prior to the primordial follicle stage with an aim of ensuring SCC in mice with advancing age. Slow degradation of SMC1β-mediated cohesion has a major role in age-dependent increase of aneuploidy (Revenkova et al, 2010). Telomeres shortened by several generations in the telomerase-null state (Liu et al., 2002b), or exposure to pharmacologically induced reactive oxygen in mice (Liu et al., 2003), produce similar abnormalities in meiotic spindles, with asymmetry and congression failure (Battaglia et al., 1996).

Oocytes contain a maternally transmitted pool of mitochondria throughout the reproductive process, including the initiation and progression of preimplantation embryo development. This pool may be involved in oocyte development, and may be required for the modulation of sperm-triggered calcium oscillations (Dumollard et al., 2007). Denham Harman was the first to hypothesize that the dysfunction of mitochondria, which constitute the main cellular site of ROS production, could be responsible for aging, due to progressive accumulation of oxidative damage (Harman, 1956, 1972). Though sufficient evidence is lacking to show a causal connection between mitochondrial DNA damage, ROS production, and aging, the free radical theory remains one of the best explanations for aging. Thouas and co workers (Thouas et al., 2005) studied the developmental ability of both young and aged oocytes, in the event of mitochondrial injury, with an aim to determine the impact of mitochondrial dysfunctions on oocyte alterations observed in aging females. The researchers ascertained a decline in blastocyst development in both groups with this trend being sudden in aged embryos. Therefore, they proposed that, due to their greater sensitivity to mitochondrial damage, aged oocytes should be protected against the potential damage of IVF procedures. Despite the possibility of being abrogated by the transfer of injured germinal vesicles (GV) into healthy ooplasts, compromised developmental potential as a result of induced mitochondrial damage in young oocytes at GV stage (Takeuchi et al., 2005) further supports the involvement of mitochondria in the reduced developmental potential of aged oocytes.

As confirmed by the observations referred to above, age-related ooplasmic dysfunction can be corrected by germinal vesicle transplantation, or micro-aspiration and transfer of ooplasm from younger eggs to older eggs. Preliminary studies suggest that novel IVF-based methods, including the transfer of mitochondria, have some clinical efficacy in rejuvenating

fertility in older women (Malter & Cohen., 2002). However, the development of these highly invasive methods in ART requires a better understanding of processes that involve mitochondrial DNA replication and transcription, since asynchrony between mitochondrial and nuclear genomes could lead to problems in mitochondrial function, localization, and biogenesis (Harvey et al., 2007). Oocyte aging being a result of oxidative stress, in other words, a consequence of accumulated damage caused by increased levels of reactive oxygen species (ROS), is the most widely accepted proposal related to reproductive aging (Harman 1956; Tarin, 1995). It has been demonstrated that the expression of genes, including oxidative stress genes, differs between aged and younger oocytes (Hamatani et al., 2004, Steuerwald et al., 2007). Oxidative stress genes downregulated in aged oocytes belong to the family of thioredoxins, which are ATP-binding proteins that act as antioxidants against oxidative stress-induced apoptosis. The hypothesis that aging is related to decreased antioxidant defenses is supported by findings in mice. It has been observed that mature oocytes from aged mice display decreased activity levels of glutathione (GSH) and GSH-transferase (Tarin et al., 2004), which are factors that play an important role in cellular defense against ROS. In addition to endogenous ROS, oocytes may also be damaged by those produced in the follicular microenvironment during their prolonged stay in the ovary and/or as a consequence of a compromised oxygen supply (van Blerkom, 2000). Available data on how ROS production and mitochondrial function contribute to replicative senescence remains limited (Passos & von Zglinicki, 2005). Research has demonstrated that accelerated telomere shortening is observed under increased oxidative stress, and that this could be reversed by antioxidants (Xu et al., 2000, Bar-Or et al., 2001). Damage-induced telomere shortening cannot be attributed solely to the induction of double-strand breaks, yet, unrepaired nucleotide or base damage of telomeres increases the proportion of unreplicated ends. Furthermore, it has been confirmed by Honda and colleagues that telomere single-strand-break frequency and shortening rate are positively correlated with each other (Honda et al., 2001a, 2001b). It remains unclear how the existence of single-strand breaks accelerates telomere shortening and why single-strand break repair is less efficient in telomeres compared to the interstitial noncoding regions of the genome (von Zglinicki, 2002). The prolonged interval between the birth of oocytes and ovulation (up to 45 years in some women) would also render oocytes susceptible to telomere independent replicating shortening, as guanine rich sequence and location in the nuclear membrane make telomeres susceptible to reactive oxygen species (ROS). Keefe and co workers suggested that telomeres provide a cytogenetic mechanism to explain the "two hits" of aging on the female reproductive system, one active during fetal life and the other during adult life (Keefe et al., 2006). Increased mitochondrial DNA (mtDNA) mutations from chronic exposure to ROS during the prolonged interval between the birth of oocytes and ovulation shorten telomeres in oocytes from older women. Short telomeres cause a reduced number of chiasmata, as well as abnormal meiotic spindles in oocytes, cell cycle arrest and apoptosis, and clinically, result in infertility, miscarriage, birth defects and cytogenetic abnormalities in embryos.

3.2.2 Depletion of ovarian follicles

Age-related changes in the human ovary involve not only oocyte aging with decline in oocyte genomic stability that leads to aneuploidy, but also the depletion of ovarian follicles (Faddy et al., 1992; Faddy, 2000; Hassold & Hunt, 2001). During fetal life the ovaries have a

stock of follicles, which should serve throughout the woman's reproductive lifespan. Besides the possible presence of germ stem cells in the postnatal ovary (Johnson et al., 2004; Liu et al., 2007), the number of follicles reduces exponentially, with a marked increase in the rate of disappearance from age 37–38 years onwards. When the supply drops below a thousand follicles, a number insufficient to sustain the cyclic hormonal process necessary for menstruation, menopause occurs at a mean age of 51 years (Faddy et al., 1992).

The timing of the menopause-related consequence of depletion of oocyte reserves, which occurs any time between 40-60 years of age (Kato et al., 1998; te Velde & Pearson, 2002; Toner et al., 1991; Baker, 1963), displays a large amount of inter-individual variability. The risk of conceiving a trisomic pregnancy, similarly, displays inter-individual variability (Warburton et al., 2004; Nicolaides et al., 2005). This natural variation in reproductive aging may be the result of environmental and genetic factors that affect individual rates of cellular aging. Although several environmental factors have been proposed as risk factors for the early onset of menopause (Brambilla & McKinlay 1989; Cramer et al., 1995; Kline et al., 2000; Pines et al., 2002), factors influencing the timing of menopause are not well understood (Snieder et al., 1998). Some genetic factors have recently been proposed to be determinants of the age at which menopause occurs. This idea is strongly supported by the following studies; the twin study which showed that the onset of menopause is genetically determined, yielding a heritability for age at menopause of 63% (Whelan et al., 1990); the study on the correlation between the menopausal age of mother and daughter (Torgerson et al., 1997); and another study which ascertained family history as a predictor of early menopause (Cramer et al., 1995). Based on animal model research and epidemiological studies in human populations, it has been proposed that longevity is associated with prolonged reproductive lifespan. It has been reported that women living till a minimum age of 100 years are greater than four times more likely to have given birth while in their 40s, compared to women living to the age of 73 (Perls et al., 1997). Several alternative mechanisms have been proposed for the relationship between longevity and age at menopause: (i) positive effect of prolonged estrogen exposure in association with later menopause on life expectancy (Perls et al., 1997), (ii) direct effect of effective ovarian age on longevity (Hsin & Kenyon, 1999; Cargill et al., 2003) or (iii) positive selection for women with slower rates of cellular aging by the use of selective pressures for maximizing female reproductive years by slow reproductive aging (Perls & Fretts, 2001; Perls et al., 2002). As their length declines with each cell division, telomeres are accepted as a marker for cellular aging. Telomere length varies among individuals (Hastie et al., 1990) and it is suggested that it may have a role in the variability observed in reproductive aging. The variability of telomere length may arise from differences in telomere length at conception, telomerase activity during early development, rate of cell division and rate of telomere loss per cell division.

Telomeres shorten by at least two mechanisms, including replicative senescence and response to damage from reactive oxygen (Passos & von Zglinicki 2005). As oocytes do not divide in adults, replicative senescence does not seem agreeable for them. However, female primordial germ cells divide during fetal life before entering meiosis. Inter-individual variations of telomere length in primordial germ cells may result from different sizes of follicular pools, and shorter telomeres may limit mitotic capacity during fetal development, reducing the size of the follicular pool (Keefe et al., 2006, Aydos et al., 2005). Previous

studies have shown that telomere length is a strong predictor of the developmental potential of sister oocytes from women undergoing in vitro fertilization procedures (Keefe et al., 2007) and is also correlated with reproductive lifespan in women (Aydos et al., 2005). Research conducted by Keefe and co workers on sister eggs, aspirated during clinical in vitro fertilization procedures, demonstrated that, compared to patient age and other clinical parameters, telomere length is a more reliable indicator of pregnancy outcome following in vitro fertilization procedures, even in cases where telomere length is measured in only spare eggs. It was determined that, telomere length in chromosomes from spare eggs was strongly correlated with that in their associated first polar bodies (R2 = 0.98). Therefore, it was considered that the telomere length of the actual embryo transferred could be estimated with greater accuracy in the future, compared to estimations based on the measurement of telomere length in a spare, sister oocyte (Keefe et al, 2004). Data obtained in a study carried out by Aydos et al revealed that telomere lengths of women at the same age were correlated with their reproductive life span. Dorland et al. (Dorland et al., 1998) studied general aging, ovarian aging and telomere length. In this study, women older than 34 years of age, who presented with unexplained infertility and had less than five oocytes following an induced cycle, were investigated. The women's reproductive lifes were accepted to cease soon. The researchers expected that if there was a relation between general aging and ovarian aging, women who were accepted to have aged ovaries would have shorter telomeres than the fertile women included in the control group. The contradictory results obtained were surprising. These results showed that, in the case of infertile women, cell divisions in all cells were less than that observed in the control (fertile) group. This was attributed to growth hormone deficiency. This study also showed that reproductive life span and telomere length were correlated with each other. Results were interpreted such that, in the presence of factors with negative impact on reproductivity and cell division, the mitotic capacity of cells would decrease. Accordingly, cells, in general, including leukocytes and primordial germ cells, divided less, and thus less primordial follicles were formed. For this reason, these women had less ovarian follicles, aged ovaries and also long leukocyte telomeres. Increased telomere length in premature ovarian failure (POF) reported in the study of Hanna et al, similar to the study conducted by Dorland et al, was explained by longer telomeres in blood, reflecting fewer mitotic divisions in the initial germ cell pool, which could also explain a smaller follicular pool and early menopause in POF patients (Hanna et al., 2009).

4. Conclusion

Aging, a normal biological process, which involves the cumulative deposition of damaged and defective cellular components, loss of cell or organ physiological functions and inability to perform physical activity also includes telomere shortening. Although aging affects female reproductive function more evidently then male, declining in fertility and conception rate, meiotic dysfunction, birth defects, increase failure rate of implantation, fertilization and resulting unsuccess outcome of pregnancy that are performed assisted reproduction techniques are seen both in men and women as a result of reproductive aging. In men spermatogenesis and reproductive functions gradually decline with aging. It was shown that semen parameters begin to decline after 35 years of age. Numerical and structural aberrations, DNA fragmentation in sperm chromosome also increases with paternal age (Vagnini et al., 2007; Plastira et al., 2007; Dunson et al., 2004). As a result, male fertility also

decreases substantially in the late 30s and continues to decrease after the age of 40 (Dunson et al., 2004). Though telomere theory of reproductive aging proposed by Keefe and co workwers does not explain the aging of reproductive function in male, as telomere length is maintained by telomerase activity and telomere attrition of germ cells is not evident in men, this theory is appropriate for female reproductive aging. According to this theory, telomere dysfunction in oocytes is responsible for several reproductive changes including meiotic dysfunction, increased aneuploidy resulting in miscarriage, decreased fertility rate and birth defects. In older women, the prolonged exit of oocytes from the production line and their chronic exposure to reactive oxygen results in the shortening of telomeres. In return, the shortening of telomeres brings about a reduction in chiasmata, the presence of abnormal meiotic spindles in oocytes, as well as cell cycle arrest, apoptosis and cytogenetic abnormalities in resulting embryos (Keefe et al., 2006). Age-related changes in the human ovary involve not only oocyte aging with decline in oocyte genomic stability that leads to aneuploidy, but also the depletion of ovarian follicles (Faddy et al., 1992; Faddy, 2000; Hassold & Hunt, 2001). During fetal life the ovaries have a stock of follicles, which should serve throughout the woman's reproductive lifespan. Besides the possible presence of germ stem cells in the postnatal ovary (Johnson et al., 2004; Liu et al., 2007), the number of follicles reduces exponentially, with a marked increase in the rate of disappearance from age 37–38 years onwards. When the supply drops below a thousand follicles, a number insufficient to sustain the cyclic hormonal process necessary for menstruation, menopause occurs at a mean age of 51 years (Faddy et al., 1992). The timing of the menopause-related consequence of depletion of oocyte reserves, which occurs any time between 40-60 years of age (Kato et al., 1998; te Velde & Pearson, 2002; Toner et al., 1991; Baker, 1963), displays a large amount of inter-individual variability. This may be also explained by telomere length. Female primordial germ cells divide during fetal life before entering meiosis. Inter-individual variations of telomere length in primordial germ cells may result from different sizes of follicular pools, and shorter telomeres may limit mitotic capacity during fetal development, reducing the size of the follicular pool (Keefe et al, 2006, Aydos et al 2003). Previous studies have shown that telomere length is a strong predictor of the developmental potential of sister oocytes from women undergoing in vitro fertilization procedures (Keefe et al., 2007) and is also correlated with reproductive lifespan in women (Aydos et al., 2005). Therefore, telomeres most likely play a crucial role in female reproductive aging. However, the molecular mechanisms of telomere regulation in early and late meiosis need to be clarified not only for a better understanding of normal development but also of human diseases associated with female reproductive aging as well.

5. References

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