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Is there a Relationship of Causality between Telomere Shortening and Aging?

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Abstract

It has been postulated that telomere shortening is a main cause of cell proliferative senescence and of organism aging. This statement is based on the following propositions: The number of divisions of cells in vitro is inversely related with the age of the donor, telomere length is reduced during divisions of cells in vitro, hence telomere length is inversely related with age of the donor. The propositions, however, have not been ascertained.

Introduction

An almost infinite number of attempts have been made to identify a mechanism responsible for the limited proliferation potential of normal human cells. One modification has particularly drawn the attention of gerontologists it concerned the shortening of chromosome ends - the telomeres. One can still see claims in the literature that this is one of the main causes of aging of mitotic cells and of the organism. The hybridization of the terminal restriction fragments (TRF) of DNA from serially dividing human fibroblasts in vitro with the appropriate probe showed a shortening of the hybridization signal with increased number of cell population doublings (Harley 1991). The extension of the human fibroblasts' doubling potential accompanied by an increase in the hybridization signal after the introduction of telomerase by transfection of the cells with vectors encoding the human telomerase catalytic unit, supported the relationship of causality between telomere shortening and the cell's finite division potential (Bodnar et al 1998).Since some immortal cell lines express the enzyme telomerase and develop the capacity to reconstitute telomeres after replication, the link between telomere integrity and replication potential seemed established.

Extrapolation from in vitro experiments to in vivo events led to equate telomere shortening with aging of the organism. The reasoning was based on the following propositions: The number of divisions of cells in vitro is inversely related with telomere length and with the age of the donor, hence telomere length is inversely related with age of the organism. To establish a relationship of causality between telomere shortening, cell doublings, and organism aging, is an oversimplification because the propositions have not been ascertained.

Moreover there cannot be one sole cause for the limited division potential. At each division cells are modified because cell division and DNA synthesis are asymmetric (Macieira-Coelho et al 1982; Macieira-Coelho 1995A, 2007). Moreover, during division there are reorganizations in the different hierarchical DNA structures that are unpredictable (Macieira-Coelho 1990) and must inevitably lead to a change in the cells and a decreased probability of initiating the cell cycle.

Number of Cell Divisions and Donor's Age

It was thought that the rational for the use of cell cultivation in vitro to study aging depended upon an inverse correlation between the number of cell population doublings and the age of the donor. A correlation could be found in some studies, but not in others. This correlation is hard to ascertain because of the difficulty of standardizing in vitro culture methods. Human adult skin fibroblasts from the papillary layer have an increased proliferation potential *in vitro* compared to reticular fibroblasts from the same biopsy (Harper and Grove, 1979; Azzarone and Macieira-Coelho, 1982). If this feature is not taken into account, which was rarely done, it is futile to find a correlation.

It is also difficult to standardize the number of doublings during the long-term maintenance of such heterogeneous cell populations because of inevitable daily technical errors of manipulation. Since cells are carried regularly with what is called 1:2 splits it was considered that the population doubles at each subculture. However, each sub-cultivation does not correspond to a population doubling because the maximal cell density reached declines after each subculture (fig. 1).

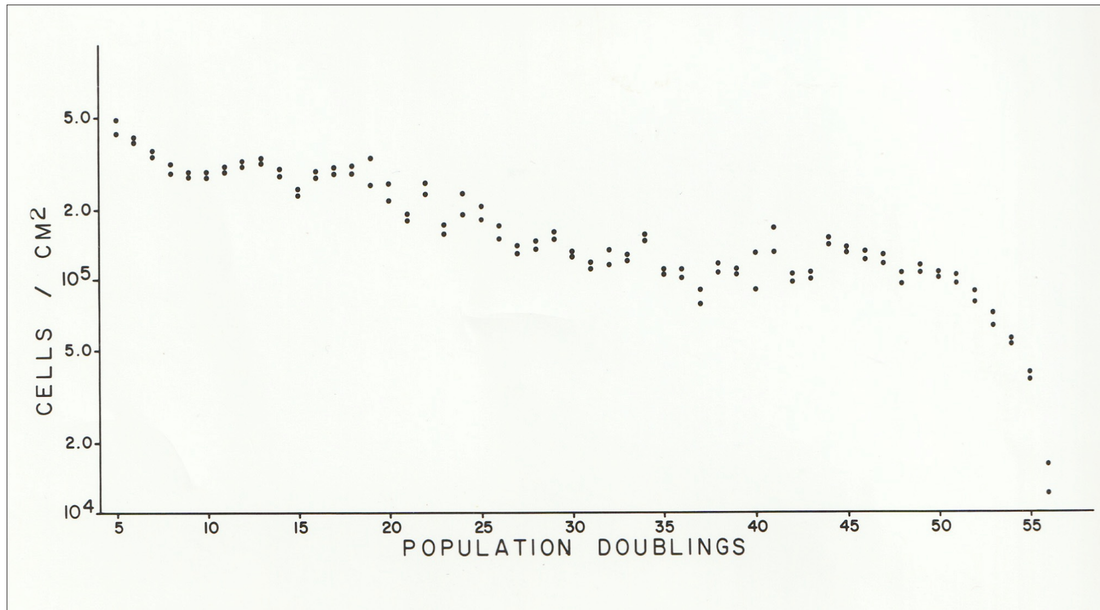

Fig 1. *Survival curve of a human fibroblast cell population. Each point represents the number of cells at resting phase after each sub-cultivation. Two cell counts were made before each subculture.*

Attempts have been made to device mathematical formulae to evaluate the number of doublings; they ignored the nature of the kinetics of proliferation of the cell population. During one passage some cells divide 2 or 3 times, others only once, others do not divide but do it only during the following passage (Macieira-Coelho 1967; Macieira-Coelho and Azzarone 1982). Some cells are slow dividers but can become fast dividers (Absher et al 1974). Hence at the level of the cell population the situation is probabilistic and chaotic it renders an exact calculation of the number of doublings meaningless.

There are other parameters that render the detection of a correlation difficult, they concern the physiopathology of the donors; certain conditions decrease (Goldstein et al 1978) and others such as the presence of a neoplastic process increase (Macieira-Coelho 2003) the division potential of connective tissue fibroblasts. Cells can also regenerate to a certain extent the long-term division potential during resting phase (reviewed in Macieira-Coelho 1988). Rubin (1997) has reviewed the studies attempting to ascertain the cell proliferation rate through the organism life span. He concluded that the basic thrust of the studies of mitotic rates indicated a gradual decline with age in adult life in mitotic frequencies of most organs. But trying to establish a strict correlation between number of doublings in vitro and donor's age is another matter. Furthermore, cells do not exhaust their proliferation potential during the life span of the organism indeed cells from old donors keep their proliferative capacity (Maier 2007).

The utilization of a lysosomal enzyme (Dimri et al1995) to identify post-mitotic cells led to the belief that they accumulate with aging in vivo. However, lysosomal enzymes accumulate in resting phase cells regardless whether the phase is reversible or irreversible (Macieira-Coelho et al 1971). So they are an unreliable marker to identify post-mitotic cells. Other more reliable markers revealed that post-mitotic cells accumulate only in pathologic conditions (Macieira-Coelho 1995B). Those believing that they are studying aging through the analysis of post-mitotic cells are in fact investigating human pathology. The same could be said of atherosclerosis and of other diseases.

Hence the first proposition - the relationship between

cell doublings in vitro and donor's age - is a moot point.

Anyway the putative correlation between number of cell divisions in vitro and aging of the donor is irrelevant. The seminal finding of the experiments of Hayflick and Moorhead (1961) and Hayflick (1965) for explaining aging of the organism is the fact that cells are modified through division changing their function and the interaction with other cells, which modifies continuously the whole organism (Macieira-Coelho 1988). The fundamental implication for aging is not the loss of the capacity of dividing but rather the deregulation of the probability of initiating the cell cycle through the modifications caused by serial divisions (Roth and Adelman 1974). This was an important conclusion at the time when, because of the semi-conservative synthesis of DNA, it was thought that sister cells were identical.

Telomere Length and Number of Cell Divisions

The other proposition mentioned above– that telomere shortening accompanies cell division -has also not been ascertained.At least in one study early-senescing human skin fibroblasts in vitro did not demonstrate accelerated telomere shortening (Ferenac et al 2015). Moreover, the erosion of telomeres through cell division is not universal. The division potential in vitro of normal human uroepithelial cells (Belair et al 1997),oral keratinocytes (Kang et al 1998; Rheinwald and Green 2002), astrocytes (Evans et al 2003),and fetal ventricular cardiomyocytes (Ball and Levine 2005) is independent of telomere size. Results obtained with normal lymphocytes vary with the laboratory and the methodology. Some investigators found that telomeric sequences are lost in proliferating lymphocytes (Vaziri et al 1993), others could not find any alteration in chromosome ends (Luke et al 1994; Kormann-Bortolotto et al 1996).

In mice size seems largely unchanged through somatic cell divisions (Kipling and Cook 1990). In Mus spretus telomere lengths have approximately the same length as in humans (Coviello-McLaughlin and Prowse 1997); the data suggested that telomere lengths could decrease due to factors other than the end replication problem during cell division.

In benign leiomyoma tumors telomere size is unrelated with the proliferation potential (Rogalla et al 1995). In malignant human tissues results are variable. Non-isotropic Southern hybridization revealed a reduction of telomere repeat arrays in 14 of the 35 tumors analyzed. In other cases 60% showed either no reduction or an increase in telomere length (Schmitt et al 1994).

Hamster embryonic fibroblasts express telomerase throughout their replicative life span and the average telomere length does not decrease in senescent cells (Carman et al 1998).

There are other caveats concerning the relationship between telomere shortening and proliferation. Human fibroblasts maintained in the presence of 3% O_2 instead of the usual concentration of 20%, have an increased proliferation potential but have shorter telomeres (Betts et al 2008). Radiation induced senescent-like growth arrest is independent of telomere shortening (Suzuki et al 2001). No significant (Chen et al 2001) or only a slight telomere shortening (Magalhaes et al 2004) was observed in senescent-like induced growth arrest of human fibroblasts after H_2O_2 stress.

The telomeres of human fibroblast chromosomes were analyzed with the canonical probe that detects all telomeres and with a TelBamm 11 probe that is specific for a subset of human telomeres (Ben 1997). The heterogeneity of fragment size was much greater when the canonical probe was used, relative to that seen using the TelBamm 11 probe. This could be due to a greater variability in the location of the restriction enzyme sites leading to chromosome rearrangements rather than to differences in the length of terminal repeats. Telomere-promoted recombination can lead to degeneration of the telomere sequence and subsequent loss of the hybridization ability (Ashley and Ward 1993). Indeed, several examples of apparent terminal deletions are actually sub-telomeric translocations (Meltzer et al 1993). Therefore the exact nature of the modifications occurring in telomeres during proliferation has yet to be ascertained.

Blackburn (2000) considered that the structure of telomeres is more important than their length, in particular the capping of the chromosome ends by a protein complex and telomerase avoiding non-homologous end-joining is critical for cell division. Some alleles code for a telomerase that can permit continued proliferation with short telomeres. Human telomerase allows cell proliferation without requiring lengthening of telomeres (Zhu et al 1999). Indeed proliferative senescence is induced by altered telomere state, not telomere loss (Karlseder et al 2002).

In summary what happens at chromosome ends during proliferation has yet to be demonstrated.

Telomere Length and Donor's Age

In nonagenarians centromeric and telomeric repeats were found to be stable (Luke et al 1994).In human tissues sperm has a TRF longer than 23 kb, which increases slightly with donor age (Allsop et al 1992).

Human telomere lengths did not show a clear correlation with tissue renewal times in vivo and are characteristic of each human individual (Takubo et al 2002); moreover the rate of telomere loss slows throughout the human life span (Unryn et al 2005). Several variables influence the telomere length during the human life span, such as the father's age at the birth of the offspring (Holohan et al 2015). In saliva samples telomeres showed a negative correlation with age up to 75 years,later age positively correlated with longer telomeres (Lapham et al 2015). Furthermore, centenarians were able to maintain long telomeres and telomere length was not a predictor of successful aging in centenarians and semi-supercentenarians (Arai et al 2015).

A large review study concluded that more studies examining the relationship between telomere length, normal aging, and mortality are required (Mather et al 2011). The same authors did not find associations between telomere length and indicators of physical function (Mather et al 2010).

Different pathologies influence telomere length. Telomeres were causally connected with mutations in the *DKC1* gene detected in a rare inherited form of bone marrow failure. The gene encodes a protein of the telomerase complex. Moreover, telomeres were found to be short in many patients with inherited or apparently acquired aplastic anemia; mutations affecting telomerase have been identified in these forms of aplastic anemia; telomerase mutations also have been associated with fibrosis of the lungs and the liver(Calado and Young 2009). Leucocyte telomere length was also found to be associated with atherosclerosis in adults (Benetos et al 2013). In the same study telomere length was found to be highly variable at birth with a rapid attrition during the first 20 years of life and virtually anchored to a given rank in adults with the passage of time. Stress is another parameter affecting telomere length; stress exposure in intrauterine life is associated with shorter telomere length in young adulthood (Entringer et al 2011).In an extensive study inflammation rather than telomere length predicted successful aging (Arai et al 2015). In scleroderma patients the loss of telomere length was not related with age or the duration of the disease, it may reflect a genetic predisposition for chromosomal instability (Artlett et al 1996). Fibroblasts from patients with Werner's syndrome, which have a shorter life span than those of normal age-matched control donors do not have shorter telomeres than control cells (Schultz et al 1996). The mean terminal repeat fragments of cells from patients with Werner's syndrome that had ceased replication were significantly longer than those of the controls. This can be interpreted in terms of the deviation from normal development that characterizes the Werner syndrome, rather than premature aging. Experiments performed with cells from Hutchinson-Gilford progeria syndrome showed that telomere length is related to factors other than replication (Decker et al 2009). Telomere length was reduced in fibroblasts and was variable; in contrast in hematopoietic cells it was within the normal range. These date raise the possibility that lamin A, which is mutated in this syndrome and is expressed in fibroblasts but not in hematopoietic cells, decreases telomere length. Diabetes-related conditions such as chronic hyperglycemia and related oxidative stress and inflammation were repeatedly associated with accelerated telomere shortening (Krasnienkov et al 2018).

Long telomeres, short cell replicative aging in vitro and short longevity is found in either wild mice or inbred laboratory strains (Kipling and Cook 1990). The size seems largely unchanged during the animal's life span. Telomere biology seems to vary with the species in a way unrelated with aging and with the respective cells proliferation life span in vitro (Kakuo et al 1999).

In another phylum, Paramecium caudatum, no shift in telomerase activity or telomere length was observed at the point of maturation; telomere elongate successively as cells divide (Takenaka et al 2001). On the other hand in P. Tetraurelia, the length of telomeres is kept constant during the life span.

Hence the majority of data in different species do not support the suggestion that telomere length has implications for aging of the organism.Factors other than aging influence telomere length.

Conclusion

A relationship between cell population doublings and donor's age has not be ascertained.

For the moment there is no proof that the reduction of the hybridization signal in TRF corresponds always to a reduction in telomere size.

The relationship between the reduction of the hybridization signal and cell division is not universal.

The suggestion that what happens with telomeres during the life span of the human organism has any connection with aging lacks experimental evidence.

Different physiopathologic conditions affect telomere size.

References

[1] Absher PM, Absher RG, Barnes WD. Genealogies of clones of diploid fibroblasts: cinematographic observations /*of cell division patterns in relation to population age. Exp Cell Res 1974; 88:95-104.

[2] Allsop RC, Vaziri H, Patterson C, Goldstein S, Younglali EV, Futcher AB, et al. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 1992; 89:10114-10118.

[3] Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, et al. Inflammation, but not telomere length, predicts successful aging at extreme old age: A longitudinal study of semi-supercentenarians. EBioMedicine 2015; 2:1549-1558.

[4] Artlett CM, Black CM, Briggs DC, Stevens CO, Welsh KI . Telomere reduction in scleroderma patients: A possible cause for chromosomal instability. Rheumatology 1996; 35:732-737.

[5] Ashley T, Ward DC. A "hot spot" of recombination coincides with an interstitial telomeric sequence in the Armenian hamster. Cytogenet Cell Genet 1993; 62:169-176.

[6] Azzarone B, Macieira-Coelho A. Heterogeneity of the kinetics of proliferation within human skin fibroblasts cell populations. J Cell Sci 1982; 57:177-187.

[7] Ball AJ, Levine F. Telomere-independent cellular senescence in human fetal cardiomyocytes. Aging Cell 2005; 4:21-22.

[8] Belair CD, Yeager TR, Lopez PM, Reznikoff CA. Telomerase activity: A biomarker of cell proliferation, not malignant transformation. Proc Natl Acad Sci USA 1997; 13677-13682.

[9] Ben P. Aging chromosome telomeres: parallel studies with terminal repeat and telomere associated DNA probes. Mech Ageing Dev 1997; 99:153-166.

[10] Benetos A, Kark JD, Susser E, Kimura M, Sinnreich R, Chen W, et al. Tracking and fixed ranking of leucocyte telomere length across the adult life course. Aging Cell 2013; 12:615-621.

[11] Betts DH, Perrault SD, King WA. Low oxygen delays fibroblast senescence despite shorter telomeres. Biogerontology 2008;9:19-31.

[12] Blackburn EH. Telomere states and cell fates. Nature 2000; 408:53-55.

[13] Bodnar AG, Ouelette M, Frolkis M, Holt SE, Chiu CP, Mrin GB, et al. Extension of life span by introduction of telomerase into normal human cells. Science 1998; 279:349-352.

[14] Calado RT, Young SN. Telomere Diseases. New Engl J Med 2009; 361:2353-2365

[15] Carman TA, Afshari CA, Barrett JC. Cellular senescence in telomerase-expressing Syrian hamster embryo. Exp Cell Res 1998; 244:33-42.

[16] Chen QM, Prowse KR, Tu V, Purdom S, Linskens HK. Uncoupling the senescent phenotype from telomere shortening in hydrogen peroxide-treated fibroblasts. Exp Cell Res 2001; 265:294-303.

[17] Coviello-McLaughlin G, Prowse KR. Telomere length regulation during postnatal development and ageing in mus spretus. Nucleic Acids Res 1997; 25:3051-3058.

[18] Decker LM, Chavez E, Vulto L, Lansdorp PM. Telomere length in Hutchinson-Gilford Progeria syndrome. Mech Ag Dev 2009; 130:377-383.

[19] Dimri G, Lee G, Basile M, Acosta M, Scott G, Roskelly C, et al. A biomarker that identifies senescent

human cells in culture and in aging skin in vivo. Proc Natl Acad Sci USA 1995; 92:9363-9367.

[20] Entringer S, Epel ES, Kumsta R, Lin J, Hellhamer DH, Blackburn EH, et al. Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. Proc Natl Acad Sc USA 2011; 108:E515-E518.

[21] Evans RJ, Wyllie FS, Wynford-Thomas D, Kipling D, Jones CJ. A p-53-dependent, telomere-independent proliferative life span barrier in human astrocytes consistent with the molecular genetics of glioma development. Cancer Res 2003; 63:4854-4861.

[22] Ferenac M, Polancec D, Huzac M, Pereira-Smith OM, Rubeli I. Early-senescing human skin fibroblasts do not demonstrate accelerated telomere shortening. J Gerontol A Biol Sci Med Sci 2015; 7:820-829.

[23] Frenck RW Jr, Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci USA 1998; 95:5607-5610.

[24] Goldstein S, Moerman EJ, Soeldner JS, Gleason RE, Barnett DM. Chronologic and physiologic age affect replicative life span of fibroblasts from diabetic, prediabetic and normal donors. Science 1978; 199:781-783.

[25] Harley CB. Telomere loss: mitotic clock or genetic time bomb. Mutat Res 1991; 256:271-283.

[26] Harper RA, Grove G. Human skin fibroblasts derived from papillary and reticular dermis: differences in growth potential in vitro. Science 1979; 4:526-527.

[27] Hayflick L. The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 1965; 37:614-636.

[28] Hayflick L, Moorehead, PS. The serial subcultivation of human diploid cell strains. Exp Cell Res 1961; 25:585-621.

[29] Holohan B, De Meyer T, Batten K, Mangino M, Hunt SC, Bekaert S, et al. Decreasing initial telomere length in humans intergenerationally understates age-associated telomere shortening. Aging Cell 2015; 14:669-677.

[30] Kakuo S, Asaoka K, Ide T. Human is a unique species among primates in term of telomere length. Biochem Biophys Res Comm 1999; 263:308-314.

[31] Kang MK, Guo W, Park NH. Replicative senescence of normal human oral keratinocytes is associated with the loss of telomerase activity without shortening of telomeres. Cell Growth Differ 1998; 9:85-95.

[32] Karlseder J, Smogorzewska A, de Lange T. Senescence induced by altered telomere state, not telomere loss. Science 2002; 295:2446-2449.

[33] Kipling D, Cook HJ. Hypervariable ultra-long telomeres in mice. Nature 1990; 347:400-402.

[34] Kormann-Bortolotto MH, Borsatto B, Smith MAC. Telomere shortening, ageing, and chromosome damage. Mech Ageing Dev 1996; 89:45-49.

[35] Krasnienkov DS, Khalangot MD, Kravchenko VI, Kovtun VA, Valserman AM. Hyperglycemia attenuates the association between telomere length and age in Ukrainian population. Exp Geront 2018; 110:247-252.

[36] Lapham K, Kvale MN, Lin J, Connell S, Croen LA, Dispensa BP, et al.. Automated assay of telomere length measurement and informatics for 100,000 subjects in the genetic epidemiology research on adult health and aging. Genetics 2015; 4:1061-1072.

[37] Luke S, Birnbaum R, Verma RS. Centromeric and telomeric repeats are stable in nonagenarians as revealed by the double hybridizarionfluorescent in situ technique. Genet Anal Tech Appl 1994; 11:77-80.

[38] Macieira-Coelho A. Influence of cell density on growth inhibition of human fibroblasts in vitro. Proc Soc Exp Biol Med 1967; 125:548-552.

[39] Macieira-Coelho.Biology of normal proliferating cells in vitro. Relevance for in vivo aging. In: Interdisciplinary Topics in Gerontology 23, pp. 1-218, Karger SA, Basel, 1988.

[40] Macieira-Coelho A. Reorganization in the different hierarchical structures of DNA during cell senescence. In: CE Finch, TE Johnson, Molecular Biology of Aging, UCLA Symposia on Molecular and Cellular Biology, 123, New York, Wiley-Liss, 1990, pp. 351-364.

[41] Macieira-Coelho A. Chaos in DNA partition during the last mitoses of the proliferative life-span of human fibroblasts. FEBS Lett 1995A; 358:126-128

[42] Macieira-Coelho A. The last mitoses of the human fibroblast proliferative life span, physiopathologic implications. Mech Ageing Dev 1995B; 82:91-104.

[43] Macieira-Coelho. Biology of Aging. Progr Molecular and Subcellular Biology 30,Heidelberg: Springer, 2003, pp. 1-192.

[44] Macieira-Coelho A. Asymmetric distribution of DNA between daughter cells with final symmetry breaking during aging of human fibroblasts. Progr Molecular and Subcellular Biology, 45, Heidelberg, Springer, 2007, pp. 227-242.

[45] Macieira-Coelho A, Azzarone B. Aging of human fibroblasts is a succession of subtle changes in the cell cycle and has a final short stage with abrupt events. Exp Cell Res 1982; 141:325-332.

[46] Macieira-Coelho A, Bengtson A, Van der Ploeg M. Distribution of DNA between sister cells during serial subcultivation of human fibroblasts. Histochemistry 1982; 75:11-24.

[47] Macieira-Coelho A, Garcia-Giralt E, Adrian M. Changes in lysosomal enzymes associated structures in human fibroblasts kept in resting stage. Proc Soc Exp Biol Med 1971; 138:712-718.

[48] Magalhaes JP, Chainiaux F, de Longueville F, Mainfroid V, Migeot V, Marcq L, et al. Gene expression and regulation in H_2O_2-induced premature senescence of human foreskin fibroblasts expressing or not telomerase. Exp Geront 2004; 39:1379-1389.

[49] Maier AB, de Koning J, Blom J, Westendorp RGJ, van Heemst D. Persistence of high-replicative capacity in cultured fibroblasts from nonagenarians. Aging Cell 2007; 6:27.

[50] Mather KA, Jorm AF, Milburn, Tan X, Easteal S, Christensen H. Associations between telomere length and sensitive indicators of physical function in mid and later life. J Gerontol A Biol Sci Med 2010; 65:792-799.

[51] Mather KA, Jorm AF, Parslow RA, Christensen H. Is Telomere Length a Marker of Aging? A Review. J Gerontol A Biol Sci Med Sci 2011; 66-202-213.

[52] Meltzer PS, Guan XY, Trent JM. Telomere capture stabilizes chromosome breakage. Nature Genet 1993; 4:252-255.

[53] Rheinwald JG, Green JH. Epidermal growth factor and the multiplication of cultured human epidermal keratinocytes. Nature 1977; 265:421-424.

[54] Rogalla P, Rohen C, Henning Y, Deichert U, Bullerdiek J. Telomere repeat fragment sizes do not Limit the growth potential of uterine leiomyomas. Biochem Biopys Res Comm 1995; 211:175-182.

[55] Roth GS, Adelman RC. Age-dependent regulation of mammalian DNA synthesis and cell division by glucocorticoids. Exp Geront 1974; 9:27-31.

[56] Rubin H. Cell aging in vivo and in vitro. Mech Ageing Dev 1997; 98:1-35.

[57] Schmitt H, Blim N, Zankl H, Schertan H. Telomere length variation in normal and malignant human tissues. Genes Chromos Cancer 1994; 101:171-177.

[58] Schultz VP, Zakian VA, Ogburn CE, McKay J, Jarzebowicz AA, Edlan SD, Martin GM. Accelerated loss of telomeric repeats may not explain accelerated replicative decline of Werner syndrome cells. Hum Genet 1996; 97:750-754.

[59] Suzuki K, Mori I, Nakayama Y, Miyakoda M, Kodama S, Watanabe M. Radiation-induced senescence-like growth arrest requires TP53 function but not telomere shortening. Radiat Res 2001; 155:248-253.

[60] Takenaka Y, Matsumura T, Hags N, Mitsui Y. Expression of telomerase reverse transcriptase and telomere elongation during sexual

maturation in Paramecium caudatum. Gene 2001; 264:153-161.

[61] Takubo K, Izumiyama-Shimomura M, Homa N, Sawabe M, Arai T, Kato M et al.Telomere lengths are characteristic in each human individual. Exp Geront 2002; 37:523-531.

[62] Unryn BM, Cook LS, Riabowoll KT. Paternal age is psotively linked to telomere length of children. Aging Cell 2005; 97:97-98.

[63] Vaziri H, Schächter F, Uchida I, Wei L, Zhu X, Effros R. Loss of telomeric DNA during aging of normal and trisomic 21 human lymphocytes. Am J Hum Genet 1993; 52:661-667.

[64] Zhu J, Wang H, Bishop JM, Blackburn EH. Telomerase extends the lifespan of virus-transformed human cells without net telomere lengthening. Proc Natl Acad Sci USA 1999; 96:3723-3728.

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