

Increasing Telomere Length

Boaz Nyona Matende B.S and Steven Petrosino Ph.D

A telomere is described as a region of repetitive nucleotide sequences that is found at both ends of a chromatid (Rufer, Dragowska, Thornbury, Roosneck, & Lansdorp, 1998)¹. Nucleotides are organic molecules such as DNA or RNA and can contain the genetic codes for life, health, and longevity. A chromatid is a copy of chromosome which is joined in the form of an “x” to another chromosome by a central structure called a centromere. Telomeres function to protect chromosomes from deteriorating or fusing with adjacent chromosomes during cell division, or mitosis (Rufer, Dragowska, Thornbury, Roosneck, & Lansdorp, 1998)². Telomeres also prevent the degradation of genes located close to the end of chromosomes by allowing the ends to shorten during replication (Rufer, Dragowska, Thornbury, Roosneck, & Lansdorp, 1998)³. Without telomeres, chromosomes would lose vital information located at their ends during cell division (Rufer, Dragowska, Thornbury, Roosneck, & Lansdorp, 1998)⁴, but the necessary shortening of the telomere has also been discovered to be the ticking of the “death clock”. As the telomere shortens, the cell prepares to die.

Telomerase and telomere length

Telomeres get consumed during cell division and, therefore, act as buffers by blocking off chromosome ends. Telomeres are replenished by the action of the enzyme **telomerase reverse transcriptase**, which is also called “**telomerase**” (Xu, Duc, Holcman, & Teixeira, 2013)⁵. The absence or diminishing levels of telomerase has been associated with the gradual shortening of telomeres (Xu, Duc, Holcman, & Teixeira, 2013)⁶. Numerous studies have established a linkage between cellular aging and telomere shortening (Xi, Li, Ren, Zhang, & Zhang, 2013)⁷. In addition, telomere attrition (or shortening) has been observed to be age-related and this has been established as critical factor in the aging process, as well as in the occurrence of many age-related

¹ Rufer, N., Dragowska, W., Thornbury, G., Roosneck, & Lansdorp, P. M. (1998). [Telomere length dynamics in human lymphocyte subpopulations measured by flow cytometry](#). *Nat Biotechnical* , 16 (8):743-747.

² Rufer, N., Dragowska, W., Thornbury, G., Roosneck, & Lansdorp, P. M. (1998).

³ Rufer, N., Dragowska, W., Thornbury, G., Roosneck, & Lansdorp, P. M. (1998).

⁴ Rufer, N., Dragowska, W., Thornbury, G., Roosneck, & Lansdorp, P. M. (1998)

⁵ Xu, Z., Duc, K. D., Holcman, D., & Teixeira, M. T. (2013). [The length of the shortest telomere as the major determinant of the onset of replicative senescence](#). *Genetics* , 194 (4):847-57.

⁶ , Z., Duc, K. D., Holcman, D., & Teixeira, M. T. (2013)

diseases (Xi, Li, Ren, Zhang, & Zhang, 2013)⁸. A pattern has been established indicating that the length of telomeres steadily declines as an individual grows older.

Other factors that are directly responsible for telomere shortening include oxidant damage and free radical load. Oxidative stress is described as the damage caused by oxidants to DNA (also called “free radicals”), cellular proteins and lipids (Genetic Science Learning Center, 2013)⁹. Oxidants are highly reactive substances that are generated during the breathing process. Oxidants are also produced due to inflammation, infection, and the consumption of alcohol and cigarettes (Genetic Science Learning Center, 2013)¹⁰. The emergence of telomere shortening as an important biomarker of aging has led to the assumption that telomere shortening might also be associated with deteriorating physical performance that is observed in aging individuals (Gardner, et al., 2013)¹¹.

Telomere shortening occurs with each cell division and replication (Rodriguez-Brenes & Peskin, 2010)¹². The progressive shortening of the telomere is directly linked to apoptosis and cellular senescence. Telomerase activity can be detected in germ cells, stem cells, and many cancerous cells. In fact, the anti-aging contribution of telomerase is hijacked by cancerous cells, which seek to become “immortal”. Scientific research suggests that when telomerase is expressed in sufficient levels in the cells, then it can immortalize or significantly extend the lifespan of the cells in question (Rodriguez-Brenes & Peskin, 2010)¹³. It is widely believed that telomeres constantly switch between two states, the capped and uncapped state. The prevailing state of the telomere defines its accessibility to telomerase and the onset of cellular senescence (Rodriguez-Brenes & Peskin, 2010)¹⁴. Using the capped state, scientists have attempted to establish a mathematical model that accounts for two processes – the regulation of telomere length

⁷ Xi, H., Li, C., Ren, F., Zhang, H., & Zhang, L. (2013). [Telomere, aging and age-related diseases](#). *Aging Clin Exp Res*, 25(2):139-46

⁸ Xi, H., Li, C., Ren, F., Zhang, H., & Zhang, L. (2013).

⁹ Genetic Science Learning Center. (2013). [Are Telomeres The Key to Aging and Cancer](#). Retrieved August 20, 2013, from The University of Utah: <http://learn.genetics.utah.edu/content/begin/traits/telomeres/>

¹⁰ Genetic Science Learning Center. (2013).

¹¹ Gardner, M. P., Ruiz, C. M., Cooper, R., Hardy, R., Sayer, A. A., Cooper, C., et al. (2013). [Telomere length and physical performance at older ages: an individual participant meta-analysis](#). *PLoS One*, 26;8(7):69526.

¹² Rodriguez-Brenes, I. A., & Peskin, C. S. (2010). [Quantitative theory of telomere length regulation and cellular senescence](#). *Proceedings of the National Academy of Sciences of the United States of America*, 107 (12):5387-5392.

¹³ Rodriguez-Brenes, I. A., & Peskin, C. S. (2010).

in telomerase positive cells and cellular senescence in aging somatic cells (Rodriguez-Brenes & Peskin, 2010)¹⁵.

A study conducted by Gardner et al. established that whereas telomere shortening in leucocytes (white blood cells) might be an important indicator of cellular aging, there is no strong evidence to show that this is a strong biomarker for physical performance (2013)¹⁶. With this knowledge, research has now shifted to establishing ways of maintaining or increasing telomere length (Xi, Li, Ren, Zhang, & Zhang, 2013)¹⁷.

A more clear review of telomere length homeostasis was carried out by Hug and Lingner (2006)¹⁸. The researchers identified that conventional DNA replication enzymes do not have the ability to replicate telomere ends (Hug & Lingner, 2006)¹⁹. Activities that take place during cell cycle cause telomere erosion. Shorter telomeres cause damage to DNA checkpoints and, therefore, mediate cellular senescence. Telomere length homeostasis utilizes telomerase, which uses an internal RNA moiety as a template to synthesize telomere repeats. Telomerase activity results in the elongation of chromosome ends, while the complementary strand is facilitated by conventional DNA polymerases (Hug & Lingner, 2006)²⁰. In human beings, telomerase is abundantly expressed during the first week of embryogenesis (the establishment and development of the human embryo), and subsequently telomerase is downgraded in most other cell types (Hug & Lingner, 2006)²¹. Correct (sufficient) telomere length is required for long term survival and prevention of premature cellular senescence and acceleration of age-linked diseases (Hug & Lingner, 2006)²². On the other hand, telomere shortening is crucial for the suppression of tumor formation by limiting the replicative capacity of cancerous cells (Hug & Lingner, 2006)²³.

In recent years, several factors that recruit telomerase to telomere in a cell cycle-dependent fashion have been identified in *Saccharomyces cerevisiae*, a yeast used in winemaking, baking and brewing (Hug & Lingner, 2006)²⁴. In humans, telomerase is thought to assemble with the telomere through mediating the formation of alternative telomere structures, in which telomere-binding proteins regulate telomerase activity by

¹⁴ Rodriguez-Brenes, I. A., & Peskin, C. S. (2010).

¹⁵ Rodriguez-Brenes, I. A., & Peskin, C. S. (2010).

¹⁶ Gardner, M. P., Ruiz, C. M., Cooper, R., Hardy, R., Sayer, A. A., Cooper, C., et al. (2013).

¹⁷ Xi, H., Li, C., Ren, F., Zhang, H., & Zhang, L. (2013).

¹⁸ Hug, N., & Lingner, J. (2006). [Telomere length homeostasis](#). *Chromosoma*, 115(6):413-25.

¹⁹ Hug, N., & Lingner, J. (2006).

²⁰ Hug, N., & Lingner, J. (2006).

²¹ Hug, N., & Lingner, J. (2006).

²² Hug, N., & Lingner, J. (2006).

²³ Hug, N., & Lingner, J. (2006).

²⁴ Hug, N., & Lingner, J. (2006).

preferentially elongating the shortest telomeres (Hug & Lingner, 2006)²⁵. In vivo analysis of telomere lengthening indicates that telomerase does not act on every telomere during the cell cycle, but shows increasing preference for telomeres depending on their length (Hug & Lingner, 2006)²⁶. Thus telomeres constantly switch between extendible and non-extendible states in a length-dependent manner (Hug & Lingner, 2006)²⁷. The researchers suggested that the level of telomerase also plays a role in the limitation of telomere length.

Increasing telomere length

There are a number of methods and factors that have been suggested to have a positive impact on telomere length. Some of these methods are based on the understanding that human lifestyles have a direct impact on telomere length while others are based on molecular activities at the cellular level (6 Tips to Maintain Telomere Length and Increase Life Expectancy, 2012)²⁸. Though this review mainly focuses on the role and effects of the antioxidant **glutathione** on telomere length, other methods that have the potential to impact on telomere length include the following: exercising for one hour at least 3 times every week; eating a healthy balanced diet; abstaining from smoking and alcohol use; dealing with stressful conditions; and sleeping for at least 7 hours a week (6 Tips to Maintain Telomere Length and Increase Life Expectancy, 2012)²⁹.

Glutathione (GSH) is described as a tripeptide that occurs as a result of the formation of a gamma peptide linkage between the glutamate side-chain carboxyl group and the amine **cysteine** (Lupton, 2004)³⁰. The amino acid cysteine (along with the mineral selenium) are rate-limiting factors in the body's ability to manufacture glutathione, and thus sufficient dietary sources of this amino acid are critical in maintaining appropriate levels of this critical antioxidant. GSH functions as an antioxidant, thereby protecting vital cell components from damage due to reactive oxygen species that include peroxides and free oxygen radicals (Lupton, 2004)³¹. Findings of several studies have

²⁵ Hug, N., & Lingner, J. (2006).

²⁶ Hug, N., & Lingner, J. (2006).

²⁷ Hug, N., & Lingner, J. (2006).

²⁸ [6 Tips to Maintain Telomere Length and Increase Life Expectancy](#). (2012, December).

Retrieved August 20, 2013, from TA-65 Blog:

<http://www.ta65doctor.com/blog/2012/12/05/maintain-telomere-length-and-increase-life-expectancy/>

²⁹ [6 Tips to Maintain Telomere Length and Increase Life Expectancy](#). (2012, December).

³⁰ Lupton, J. R. (2004). [Glutathione Metabolism and its implications for health](#). *J Nutr*, 134(3):489-92.

³¹ Lupton, J. R. (2004).

established GSH to be a master antioxidant in all cellular defense activities (Lupton, 2004)³². Glutathione also plays a crucial role in several cellular events including gene expression, cell proliferation and apoptosis, signal transduction, DNA and protein synthesis, cytokine production and immune response, in addition to protein glutathionylation (Metcalfe & Alonso-Avarez, 2010)³³.

Glutathione is produced in the liver and functions as antioxidant in various parts of the body including lungs, the liver, Red Blood Cells (RBCs), and the intestinal tract. GSH also detoxifies the body from various toxins, including those generated by heavy metals, cigarette smoking, alcohol, cancer chemotherapy, and radiation (Lupton, 2004)³⁴.

In mammalian cells, glutathione concentrations lie between 1 to 10mM, though lower concentrations predominate over its oxidized form of (GSSG). Various studies have demonstrated that maintaining an optimal ratio between GSH and GSSG plays a critical role in survival and the deficiency causes oxidative damage (Lupton, 2004)³⁵. Glutathione plays a crucial role in the control and prevention of many disorders including autoimmune diseases, diabetes, neurodegenerative diseases and cancer (Lupton, 2004)³⁶.

Glutathione is widely accepted as a **master antioxidant**. To effectively understand the role or effect of glutathione in increasing telomere length it is imperative to first understand the impact of oxidative stress on telomere length.

Oxidative stress is understood as the imbalance that takes place when the rate of production of free radicals or reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defense and repair mechanisms resulting into the oxidative damage to biomolecules (Metcalfe & Alonso-Avarez, 2010)³⁷. This concept can, however, be expanded further to include the disruption caused by the process of reduction - redox reactions that take place during cellular signaling (Metcalfe & Alonso-Avarez, 2010)³⁸.

³² Lupton, J. R. (2004).

³³ Metcalfe, N. B., & Alonso-Avarez, C. (2010). [THE ECOLOGY OF ANTIOXIDANTS & OXIDATIVE STRESS IN ANIMALS: Oxidative stress as a life-history constraint: the role of reactive oxygen species in shaping phenotypes from conception to death](#). *Functional Ecology* , 24(5):984-996.

³⁴ Lupton, J. R. (2004).

³⁵ Lupton, J. R. (2004).

³⁶ Lupton, J. R. (2004).

³⁷ Metcalfe, N. B., & Alonso-Avarez, C. (2010).

³⁸ Metcalfe, N. B., & Alonso-Avarez, C. (2010).

Taurine and telomere length

A study was conducted by Ozsarlak-Sozer et al. to investigate oxidative stress in relation to telomere length maintenance in vascular smooth muscle cells following balloon angioplasty (2011)³⁹. The study utilized a single or combined treatment of rabbits with either buthionine, sulfoximine, or the amino acid **taurine** (Ozsarlak-Sozer, Kerry, Gokce, Oran, & Topcu, 2011)⁴⁰. Exposure to oxidative stress led to an increase in the balloon injury while taurine treatment caused a significant reduction in L-buthionine-sulfoxamine-related intimal hyperplasia (Ozsarlak-Sozer, Kerry, Gokce, Oran, & Topcu, 2011)⁴¹. The findings of the study indicated that the two variables had a significant impact on telomere length and distribution.

Another closely associated study was conducted by Watfa et al (2011)⁴². The study sought to establish different markers of oxidative stress in patients with **Parkinson's disease** (Watfa, et al., 2011)⁴³. The study was based on findings of various studies that short telomeres are associated with high oxidative stress and a number of age-related diseases (Watfa, et al., 2011)⁴⁴. Parkinson's disease (PD) is an age related condition in which oxidative stress is implicated in the pathology, even though little is understood regarding its pathogenic mechanism. The objective of this case-controlled study was to investigate telomere length and the different markers of oxidative stress in elderly patients with Parkinson's disease in comparison to age control subjects (Watfa, et al., 2011)⁴⁵. The findings of the study showed a trend towards shorter telomeres in patients with Parkinson's Disease (6.06 +/- 0.81 kb in PD versus 6.45 +/- 0.73kb in controls). However, there was no significance difference observed in terms of oxidative stress markers in the two groups (Watfa, et al., 2011)⁴⁶. In the controls, age was determined as the main factor in telomere shortening, while in the PD group, telomere shortening was mainly associated with plasmatic concentrations of **carbonyl proteins** (Watfa, et

³⁹ Ozsarlak-Sozer, G., Kerry, Z., Gokce, G., Oran, I., & Topcu, Z. (2011). [Oxidative stress in relation to telomere length maintenance in vascular smooth muscle cells following balloon angioplasty](#). *J Physiol Biochem*, 6(1):35-42.

⁴⁰ Ozsarlak-Sozer, G., Kerry, Z., Gokce, G., Oran, I., & Topcu, Z. (2011).

⁴¹ Ozsarlak-Sozer, G., Kerry, Z., Gokce, G., Oran, I., & Topcu, Z. (2011).

⁴² Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011). [Study of telomere length and different markers of oxidative stress in patients with parkinson's disease](#). *J Nutr Health Aging*, 15(4):277-81.

⁴³ Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011).

⁴⁴ Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011).

⁴⁵ Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011).

⁴⁶ Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011).

al., 2011)⁴⁷. [Carbonyl proteins](#) are biomarkers for oxidative stress, and elevated levels have been observed in many other degenerative diseases including Alzheimer's disease (AD), rheumatoid arthritis, diabetes, sepsis, chronic renal failure, and respiratory distress syndrome (ARDS). The researchers concluded that in PD, telomere length was shorter because of high oxidative stress as determined by carbonyl proteins.

A study was conducted by Ksiazek et al. to investigate the vulnerability to oxidative stress and different patterns of senescence in human peritoneal mesothelial cell strains (2009)⁴⁸. The study aimed at establishing the different replicative potential in vitro of the ascites fluid-derived mesothelial cell line LP-9 and primary cultures of human omentum-derived mesothelial cells (HOMCs) (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁴⁹. It was established that HOMCs were associated with fewer cell divisions and early senescence compared to LP-9 cells (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁵⁰. This was linked to the increase in the expression of senescence-associated-beta-galactosidase and cell cycle inhibitors such as p16INK4a and p21WAF1 (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁵¹. In addition, many early-passage HOMCs had almost 3 times as more senescence associated DNA damage foci compared to LP-9. However, the foci present in HOMCs were outside telomeres, a case not seen in LP-9 (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁵². Consequently, HOMCs entered senescence with significantly lower levels of **lipofuscin** (lipofuscin is a yellow-brown pigment associated with cellular aging and damage), damaged DNA, and markedly reduced levels of glutathione (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁵³. Early-passage HOMCs were found to generate high amounts of reactive oxygen species, either spontaneously or in response to exogenous oxidants⁵⁴. The study concluded that as opposed to LP-9 cells, the

⁴⁷ Wafra, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011).

⁴⁸ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009). [Vulnerability to oxidative stress and different patterns of senescence in human peritoneal mesothelial cell strains](#). *Am J Physiol Regul Integr Comp Physiol* , 296(2):374-82.

⁴⁹ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵⁰ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵¹ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵² Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵³ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵⁴ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

HOMCs underwent stress-induced telomere-independent premature senescence, which might be due to increased vulnerability to oxidative DNA injury associated with critically reduced glutathione levels (Ksiazek, Mikula-Pietrasik, Olijslagers, Jorres, Zqlinicki, & Witowski, 2009)⁵⁵.

An *in vitro* study was conducted by Kim et al to investigate cellular senescence induced by lipopolysaccharide (LPS) in pulmonary alveolar epithelial cells (2012)⁵⁶. The study clarified that the cellular senescence phenomenon is associated with the oxidative stress effect that is induced by LPS and, therefore, investigated whether antioxidants could be used to inhibit the reduced cellular viability due to LPS (Kim, Huh, Han, & Kim, 2012)⁵⁷. During the study, the researchers established pre-apoptotic concentration of LPS using caspase activation using a Caspase-Glo 3/7 luminescence assay kit (Kim, Huh, Han, & Kim, 2012)⁵⁸. The higher concentration of LPS caused cells to have morphological characteristics that are commonly associated with senescent cells, in addition to increased senescence-linked beta galactosidase activity (Kim, Huh, Han, & Kim, 2012)⁵⁹. However, no telomere shortening was observed in association with the apoptotic LPS concentration. Glutathione was used to inhibit the ability for LPS to reduce cellular viability. The study indicated that LPS had the ability to cause cellular senescence in lung alveolar epithelial cells, a phenomenon that is closely linked to the production of hydrogen peroxide by LPS (Kim, Huh, Han, & Kim, 2012)⁶⁰.

Glutathione and telomere length studies

Glutathione has long been established as an essential antioxidant in eukaryotic cells (somatic cells containing a nucleus, and which are found in most body tissues). Studies have shown that cells with high glutathione (GSH) levels have high proliferation rates. Part of the reason is that glutathione acts on oxidative stress to ensure optimal functioning of telomerase and other crucial proteins during cell cycle. A number of studies have documented evidence of the role of enhanced glutathione levels.

⁵⁵ Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009).

⁵⁶ Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012). [Analysis of cellular senescence induced by lipopolysaccharide in pulmonary alveolar epithelial cells](#). *Arch Gerontol Geriatr*, 54(2):e35-41.

⁵⁷ Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012).

⁵⁸ Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012).

⁵⁹ Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012).

⁶⁰ Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012).

A review was contacted by Markovic et al to investigate the role of glutathione in cell nucleus (2010)⁶¹. The review was based on the finding that high glutathione levels lead to high cell proliferation. This feature is usually observed in the defense of cancer cells against chemotherapy or ionizing radiation (Markovic, Garcia-Gimenez, Gimeno, Vina, & Pallardo, 2010)⁶². The study underscored the increased interest in the role of glutathione in cell nucleus. The review concluded that glutathionylation and oxidation of nuclear proteins appear as reversible physiological mechanisms in the regulation of DNA compaction, cell cycle and DNA repair (Markovic, Garcia-Gimenez, Gimeno, Vina, & Pallardo, 2010)⁶³.

A review conducted by Pallardo et al. sought to summarize the relationship between glutathione and important cell-nucleus events that take place during the cell cycle (2009)⁶⁴. It was established that most GSH is co-localized within nuclear DNA during cell proliferation. A number of relevant nuclear proteins were found to be strictly depended on nuclear redox status (Pallardo, Markovic, Garcia, & vina, 2009)⁶⁵. For instance, the study established that telomerase activity was controlled by shifts in glutathione redox potential with values comparable to those that are seen *in vivo* (Pallardo, Markovic, Garcia, & vina, 2009)⁶⁶.

A study was carried out by Almroth et al to investigate the gender differences in health and aging of Atlantic cod subject to size and selective fishery (2012)⁶⁷. The researchers analyzed the aging parameters in both male and female Atlantic cod, *gadus morhua*, that were captured in Kattegat, Skagerrak and Oresund (Almroth, Skold, & Nilsson, 2012)⁶⁸. Males were found to possess longer liver telomeres and more marked catalase activity compared to females, while females showed higher superoxide dismutase activity, condition factor, and liver somatic index (Almroth, Skold, & Nilsson, 2012)⁶⁹. Effects of age were observed in males where the levels of glutathione (GSH) and

⁶¹ Markovic, J., Garcia-Gimenez, J. L., Gimeno, A., Vina, J., & Pallardo, F. V. (2010). [Role of glutathione in cell nucleus](#). *Free Radic Res*, 44(7):721-33.

⁶² Markovic, J., Garcia-Gimenez, J. L., Gimeno, A., Vina, J., & Pallardo, F. V. (2010).

⁶³ Markovic, J., Garcia-Gimenez, J. L., Gimeno, A., Vina, J., & Pallardo, F. V. (2010).

⁶⁴ Pallardo, F. V., Markovic, J., Garcia, J. L., & vina, J. (2009). [Role of nuclear glutathione as a key regulator of cell proliferation](#). *Mol Aspects Med*, 30(1-2):77-85.

⁶⁵ Pallardo, F. V., Markovic, J., Garcia, J. L., & vina, J. (2009).

⁶⁶ Pallardo, F. V., Markovic, J., Garcia, J. L., & vina, J. (2009).

⁶⁷ Almroth, C., Skold, M., & Nilsson, S. (2012). [Gender differences in health and aging of Atlantic cod subject to size selective fishery](#). *biol Open*, 15;1(1):922-8.

⁶⁸ Almroth, C., Skold, M., & Nilsson, S. (2012).

⁶⁹ Almroth, C., Skold, M., & Nilsson, S. (2012).

telomere length were observed to decline with age (Almroth, Skold, & Nilsson, 2012)⁷⁰. The liver somatic index rose and level of oxidized glutathione decreased with age. Though the study was aimed at drawing conclusions on the conservation of old mature cod fish, they are also indicative of the importance of high glutathione levels on telomere length.

Superoxide Dismutase (SOD) and telomere length studies

Superoxide Dismutase is present inside the cell as well as in the extra-cellular fluids. SOD is one of the primary anti-oxidant defenses within the body, and it plays a critical role in fighting destructive free radicals and in the reduction of oxidative stress (“cellular rusting”) that has been implicated in many degenerative diseases, including heart or myocardial disease. Many plants can produce both SOD and other potent antioxidants including glutathione catalase and glutathione peroxidase, primarily in the sprouts of certain vegetables and fruits. These powerful antioxidants protect the fledgling plants from numerous environmental insults. Melons are also a rich source of these glutathione and SOD enzymes, and fruits and vegetables with the highest concentrations have significantly longer shelf lives. SOD and antioxidants such as glutathione all appear to have a beneficial effect on telomere length. Makino et al. conducted a study to establish how antioxidant therapy attenuates myocardial telomerase activity reduction in superoxide dismutase-deficient mice (2011)⁷¹. The study evaluated telomere biology in heart/muscle-specific manganese superoxide dismutase-deficient mice (H/M-SOD2(-/-)) which are known to develop congestive heart failure, exhibiting pathology that is typical of dilated cardiomyopathy (Makino, et al., 2011)⁷². **EUK-8** (25mg/kg/day), a type of superoxide dismutase and catalase mimetic, was administered to the H/M-SOD2(-/-) mice for a period of four weeks beginning with the eighth week of age (Makino, et al., 2011)⁷³. Telomerase activity, telomere length, telomere associated proteins, and cell death signals were assessed in hearts of the control wild-type mice (H/M-Sod2(lox/lox)) and superoxide dismutase-deficient, H/M-SOD2(-/-) mice either treated or untreated with EUK-8 (Makino, et al., 2011)⁷⁴. No telomere shortening was observed in the heart tissues of all mice that were tested, though there was a decrease in telomerase activity in the heart tissue from H/M-SOD2(-/-) compared to control mice (Makino, et al., 2011)⁷⁵. The results of the investigation

⁷⁰ Almroth, C., Skold, M., & Nilsson, S. (2012).

⁷¹ Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011). [Antioxidant therapy attenuates myocardial telomerase activity reduction in superoxide dismutase-deficient mice.](#) *J Mol Cell Cardiol*, 50(4)670-7.

⁷² Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011).

⁷³ Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011).

⁷⁴ Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011).

⁷⁵ Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011).

suggest that oxidant stress might affect myocardial telomerase activity and associated proteins (Makino, et al., 2011)⁷⁶.

A study was conducted by Borrás et al. to investigate the role of glutathione in the regulation of telomerase activity in 3T3 fibroblasts (2004)⁷⁷. The study was based on the finding that a change in telomerase activity was associated with cancer in cases where the activity is increased, or with cell cycle arrest when the activity is reduced (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁷⁸. The study reported that glutathione, a physiological antioxidant that is found in high concentrations, regulates telomerase activity in cells in culture (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁷⁹. Telomerase activity was seen to increase prior to exponential cell growth. The peak of telomerase activity took place 24 hours after plating and coincided with the maximum level of glutathione in the cells (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸⁰. However, when the cells were treated with buthionine sulfoximine, which causes a reduction in glutathione levels in cells, telomerase activity was seen to decrease by up to 60% and, therefore, delaying cell growth (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸¹. The depletion of glutathione had a negative impact on the expression of E2F4 and Id2, which regulates the cell cycle proteins (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸². When the glutathione levels were restored following incubation with glutathione monoethylester, telomerase activity, cell cycle, and associated proteins returned to control values (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸³. The effect of glutathione redox status on the telomerase multicomplex was investigated by incubating protein extracts from fibroblasts with different glutathione redox buffers (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸⁴. Telomerase activity was found to be maximal when the reduced/oxidized glutathione ratio was high. The findings of this study underscored the key role played by glutathione in the control of telomerase activity during a cell cycle (Borrás, Esteve, vina, Sastre, vina, & Pallardo, 2004)⁸⁵.

⁷⁶ Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011).

⁷⁷ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004). [Glutathione regulates telomerase activity in 3T3 fibroblasts](#). *J Biol Chem*, 13;279(33):34332-5.

⁷⁸ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁷⁹ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸⁰ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸¹ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸² Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸³ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸⁴ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

⁸⁵ Borrás, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

Iron overload and telomeres

A study was conducted by Brown et al. to investigate the role of increased hepatic telomere activity in a rat model of iron overload (2007)⁸⁶. The study was based on the background that telomere shortening caused by proliferation or oxidative damage results in the replicative arrest and senescence, which may affect regeneration during chronic liver injury (Brown, et al., 2007)⁸⁷. Whereas there is little attention placed on experimental liver injury on telomeres, previous studies indicate that telomerase is protective in some rodent liver injury models (Brown, et al., 2007)⁸⁸. The purpose of the study was to establish the effects of **iron overload** on telomere length and telomerase activity in a rat liver (Brown, et al., 2007)⁸⁹. The mean telomere length was same in both control and iron overloaded livers. Telomerase activity increased 3 times following iron loading, with no change in levels of TERT mRNA or protein (Brown, et al., 2007)⁹⁰. A considerable increase in glutathione (1.5 fold), cysteine (15 fold), and glutamate cysteine ligase activity (1.5 fold) were seen in iron loaded livers, whereas the activity of telomerase was stopped by addition of N-ethylmaleimide (Brown, et al., 2007)⁹¹. The study was the first to demonstrate an increased telomerase activity associated with alteration of thiol in vivo (Brown, et al., 2007)⁹².

A study conducted by Eshkoo et al. investigated on the association of glutathione S-transferase mu (GSTM1) and glutathione S-transferase theta (GSTT1) with aging in auto repair workers (2012)⁹³. The study was done on 120 car auto repair workshop workers exposed to occupational hazards and 120 controls without this kind of exposure (Eshkoo, et al., 2012)⁹⁴. Multiplex PCR was used to establish the null and non null

⁸⁶ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007). [Increased hepatic telomerase activity in a rat model of iron overload: a role for altered thiol redox state?](#) *Free Radic Biol Med*, 15;42(2):228-35.

⁸⁷ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁸⁸ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁸⁹ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁹⁰ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁹¹ Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁹² Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007).

⁹³ Eshkoo, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012). [Association of GSTM1 and GSTT1 with ageing in auto repair shop workers.](#) *Genet Mol Res*, 11(2):1486-96.

⁹⁴ Eshkoo, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012).

genotypes in both GSTT1 and GSTM1. The study showed that comet tail length, micronucleus frequency, and relative telomere length differences between the null and the non-null genotypes of the GSTM1 gene were significantly greater in the exposed group (Eshkoo, et al., 2012)⁹⁵. The absence of GSTT1 was not associated with the damage on biomarkers ($P>0.05$), while the lack of GSTM1 was seen associated with greater genomic damage (Eshkoo, et al., 2012)⁹⁶. The researchers concluded that early aging could occur under the influence of GSTM1 and GSTT1 in conjunction with environmental and socio-demographic factors (Eshkoo, et al., 2012)⁹⁷. The duration of working time was highly linked telomere length, comet tail length and micronucleus frequency.

Other studies On telomere length

In addition to glutathione, there are various proteins that have been implicated to play a role in the regulation of telomere length, though some of them take place in pathological conditions. The studies reviewed below have more information on this.

Though the human telomeric repeat binding factor protein (TRF1) has been found to play an important role in the regulation, not much is understood in regard to the particular function of the protein during protein cycle (Shen, Haggblom, Vogt, Hunter, & Lu, 1997)⁹⁸. A characterization of telomeric proteins Pin2 and TRF1 conducted by Shen et al suggested that Pin2/TRF1 may connect mitotic control to the telomerase regulatory machinery whose deregulation is well established in cancer and aging (1997)⁹⁹.

A study conducted by Wang et al investigated the ability to maintain telomere length through sister chromatid exchange in murine embryonic stem (ES) cells possessing critically shortened telomeres (2005)¹⁰⁰. The study utilized telomere sister chromatid

⁹⁵ Eshkoo, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012).

⁹⁶ Eshkoo, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012).

⁹⁷ Eshkoo, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012).

⁹⁸ Shen, M., Haggblom, C., Vogt, M., Hunter, T., & Lu, K. P. (1997). [Characterization and Cell Cycle Regulation of the Related Human Telomeric Proteins Pin2 and TRF1 Suggest a Role in Mitosis](#). *Proceedings of the National Academy of Sciences of the United States of America* , 94(25):13618-13623.

⁹⁹ Shen, M., Haggblom, C., Vogt, M., Hunter, T., & Lu, K. P. (1997).

¹⁰⁰ Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005). [An Increase in Telomere Sister Chromatid Exchange in Murine Embryonic Stem Cells Possessing Critically Shortened Telomeres](#). *Proceedings of the National Academy of Sciences of the United States of America* , 102(29):10256-10260.

exchange (T-SCE) in murine telomere reverse transcriptase-deficient (mTert^{-/-}) splenocytes and ES cells (Wang, et al., 2005)¹⁰¹. The study was based on the knowledge that telomerase deficiency leads to the gradual loss of telomeric DNA in mTert^{-/-} splenocytes and ES cells, eventually leading to chromosomes that are telomere signal-free ends (SFEs) (Wang, et al., 2005)¹⁰². The study showed evidence of sister chromatid exchange in a subset of mTert^{-/-} splenocytes (spleen cells) or ES cells that possessed multiple SFEs (Wang, et al., 2005)¹⁰³. No increase in T-SCE was observed in mTert heterozygous (mTert^{+/-}). The findings of the study suggested that there are variations in the ability of both animals and cell culture to conduct genomic rearrangements as a way of maintaining telomere integrity when telomeres become critically short (Wang, et al., 2005)¹⁰⁴.

A study was conducted by Hoffmeyer et al. to establish the roll of Wnt/ β -Catenin signaling in the regulation of telomerase subunit Tert in stem cells and cancer cells (2012)¹⁰⁵. The study was based on the important function of telomerase in controlling telomere length and, thus playing a role in the control of aging, stem cells, and cancer (Hoffmeyer, et al., 2012)¹⁰⁶. The study established that embryonic stem cells that were deficient in **β -Catenin** had short telomeres, while those that with the activated form of β -Catenin had long telomeres (Hoffmeyer, et al., 2012)¹⁰⁷. The study uncovered a previously unknown association between stem cells and oncogenic potential in which β -Catenin regulates the expression of tert, and telomere length by extension (Hoffmeyer, et al., 2012)¹⁰⁸. This finding has a potential application in human cancer and regenerative therapy (Hoffmeyer, et al., 2012)¹⁰⁹.

A study was contacted by Kamranvar et al to investigate how malignant cells achieve replicative immortality by alternative mechanisms – the common one de novo synthesis of telomeric DNA by telomerase, and a rare one that is based on telomere recombination known as alternative lengthening of telomeres (ALT) (2013)¹¹⁰. The study

¹⁰¹ Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005).

¹⁰² Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005).

¹⁰³ Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005).

¹⁰⁴ Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005).

¹⁰⁵ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

[Wnt/ \$\beta\$ -Catenin Signaling Regulates Telomerase in Stem Cells and Cancer Cells](#). *Science New Series*, 336 (6088):1549-1554.

¹⁰⁶ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

¹⁰⁷ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

¹⁰⁸ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

¹⁰⁹ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

¹¹⁰ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

identified that **Epstein-Barr virus (EBV)** transforms human B-lymphocytes into lymphoblastoid cell lines that have unlimited growth potential both in vitro and in vivo (Kamranver, Chen, & Masucci, 2013)¹¹¹. The study showed that EBV-infected cells exhibited multiple indicators of telomere dysfunction which include the occurrence of extra-chromosomal telomeres, telomere fusion and telomere length heterogeneity, and also the undergoing of increased telomere length without increase in the level of telomerase activity (Kamranver, Chen, & Masucci, 2013)¹¹². The findings of the study suggested the activation of ALT by EBV infection. Newly infected cells also exhibited a significant reduction of telomere-associated TRF2 and expresses lower levels of TRF1, TRF2, POT1 and ATRX, indicating that telomere de-protection as an important factor in the activation of Alternative lengthening of telomeres ALT (Kamranver, Chen, & Masucci, 2013)¹¹³. The findings of this study show that recombinant-dependent mechanisms are involved in the maintenance of telomere homeostasis in EBV-induced B-cell immortalization (Kamranver, Chen, & Masucci, 2013)¹¹⁴.

Centenarian Studies

In studies of centenarians, elevated levels of one form of glutathione, the enzyme glutathione reductase, appears to serve as a predictor of longevity.^{115,116} Reduced levels of glutathione are associated with shortened life expectancy and with numerous degenerative diseases such as AIDS, Alzheimer's Disease, infections, COPD, osteoarthritis, and accelerated aging.¹¹⁷⁻¹²⁴

Summary

The maintenance or increase in telomere length has been established as an important factor prevention of aging and susceptibility to age related diseases. Telomerase activity is critical for optimal functioning of telomeres. Telomerase activity can be disrupted by a number of physiological conditions including oxidative stress. Glutathione is a master antioxidant and is abundantly found in the cell nucleus where it functions to eliminate oxidative stress and, thereby promote cellular functions including telomerase activity in increasing the length of telomeres. Glutathione status has been associated with reduced susceptibility to diseases of aging, increased telomere length, and with longevity in centenarians. Most of the studies reviewed above reflect this position

¹¹¹ Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012).

¹¹² Kamranver, S. A., Chen, X., & Masucci, M. G. (2013). [Telomere dysfunction and activation of alternative lengthening of telomeres in B-lymphocytes infected by Epstein-Barr virus](#). *Oncogene*, 10:1038/Onc; 189.

¹¹³ Kamranver, S. A., Chen, X., & Masucci, M. G. (2013).

¹¹⁴ Kamranver, S. A., Chen, X., & Masucci, M. G. (2013).

though others have reported on alternative methods of achieving or maintaining increased telomere length such as ALT in EBV infection.

-
- ¹¹⁵ Klapcinska B, Derejczyk J, Wieczorowska-Tobis K, et al. Antioxidant defense in centenarians (a preliminary study). *Acta Biochim Pol.* 2000;47(2):281-92.
- ¹¹⁶ Andersen HR, Jeune B, Nybo H, et al. Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. *Age Ageing.* 1998 Sep;27(5):643-8.
- ¹¹⁷ Micke P, Beeh KM, Buhl R. Effects of long-term supplementation with whey proteins on plasma glutathione levels of HIV-infected patients. *Eur J Nutr.* 2002 Feb;41(1):12-8.
- ¹¹⁸ Micke P, Beeh KM, Schlaak JF, Buhl R. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. *Eur J Clin Invest.* 2001 Feb;31(2):171-8.
- ¹¹⁹ Bishop C, Hudson VM, Hilton SC, Wilde C. A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. *Chest.* 2005 Jan;127(1):308-17.
- ¹²⁰ Carlo MD, Jr., Loeser RF. Increased oxidative stress with aging reduces chondrocyte survival: correlation with intracellular glutathione levels. *Arthritis Rheum.* 2003 Dec;48(12):3419-30.
- ¹²¹ Cho CG, Kim HJ, Chung SW, et al. Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process. *Exp Gerontol.* 2003 May;38(5):539-48.
- ¹²² Junqueira VB, Barros SB, Chan SS, et al. Aging and oxidative stress. *Mol Aspects Med.* 2004 Feb;25(1-2):5-16.
- ¹²³ Lothian B, Grey V, Kimoff RJ, Lands LC. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. *Chest.* 2000 Mar;117(3):914-6.
- ¹²⁴ Vina J, Lloret A, Orti R, Alonso D. Molecular bases of the treatment of Alzheimer's disease with antioxidants: prevention of oxidative stress. *Mol Aspects Med.* 2004 Feb;25(1-2):117-23.

This article can be found at:

http://www.nutritionadvisor.com/increasing_telomere_length_and_the_effect_of_glutathione.pdf

References

6 Tips to Maintain Telomere Length and Increase Life Expectancy. (2012, December).

Retrieved August 20, 2013, from TA-65 Blog:

<http://www.ta65doctor.com/blog/2012/12/05/maintain-telomere-length-and-increase-life-expectancy/>

Almroth, C., Skold, M., & Nilsson, S. (2012). Gender differences in health and aging of Atlantic cod subject to size selective fishery. *biol Open* , 15;1(1):922-8.

Andersen HR, Jeune B, Nybo H, et al. Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. *Age Ageing*. 1998 Sep;27(5):643-8.

Bishop C, Hudson VM, Hilton SC, Wilde C. A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. *Chest*. 2005 Jan;127(1):308-17.

Borras, C., Esteve, J. M., vina, J. R., Sastre, J., vina, J., & Pallardo, F. V. (2004).

Glutathione regulates telomerase activity in 3T3 fibroblasts. *J Biol Chem*, 13;279(33):34332-5.

Brown, K. E., Mathahs, M. M., Broadhurts, K. A., Coleman, M. C., Ridnour, L. A., Schmidt, W. N., et al. (2007). Increased hepatic telomerase activity in a rat model of iron overload: a role for altered thiol redox state? *Free Radic Biol Med*, 15;42(2):228-35.

Carlo MD, Jr., Loeser RF. Increased oxidative stress with aging reduces chondrocyte survival: correlation with intracellular glutathione levels. *Arthritis Rheum*. 2003 Dec;48(12):3419-30.

Cho CG, Kim HJ, Chung SW, et al. Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process. *Exp Gerontol*. 2003 May;38(5):539-48.

Eshkoor, S. A., Marashi, S. J., Ismail, P., Rahman, S. A., Mirnargesi, M., Adon, M. Y., et al. (2012). Association of GSTM1 and GSTT1 with ageing in auto repair shop workers. *Genet Mol Res*, 11(2):1486-96.

Gardner, M. P., Ruiz, C. M., Cooper, R., Hardy, R., Sayer, A. A., Cooper, C., et al. (2013). Telomere length and physical performance at older ages: an individual participant meta-analysis. *PLoS One*, 26;8(7):69526.

Genetic Science Learning Center. (2013). *Are Telomeres The Key to Aging and Cancer*.

Retrieved August 20, 2013, from The University of Utah:

<http://learn.genetics.utah.edu/content/begin/traits/telomeres/>

Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Valle, I. D., et al. (2012). Wnt/ β -Catenin Signaling Regulates Telomerase in Stem Cells and

Cancer Cells. *Science New Series* , 336 (6088):1549-1554.

Hug, N., & Lingner, J. (2006). Telomere length homeostasis. *Chromosoma* , 115(6):413-25.

Junqueira VB, Barros SB, Chan SS, et al. Aging and oxidative stress. *Mol Aspects Med.* 2004 Feb;25(1-2):5-16.

Kamranver, S. A., Chen, X., & Masucci, M. G. (2013). Telomere dysfunction and activation of alternative lengthening of telomeres in B-lymphocytes infected by Epstein-Barr virus. *Oncogene* , 10:1038/0nc; 189.

Kim, C. O., Huh, A. J., Han, S. H., & Kim, J. M. (2012). Analysis of cellular senescence induced by lipopolysaccharide in pulmonary alveolar epithelial cells. *Arch Gerontol Geriatr* , 54(2):e35-41.

Klapcinska B, Derejczyk J, Wieczorowska-Tobis K, et al. Antioxidant defense in centenarians (a preliminary study). *Acta Biochim Pol.* 2000;47(2):281-92.

Ksiazek, K., Mikula-Pietrasik, J., Olijslagers, S., Jorres, A., Zqlinicki, T. v., & Witowski, J. (2009). Vulnerability to oxidative stress and different patterns of senescence in human peritoneal mesothelial cell strains. *Am J Physiol Regul Integr Comp Physiol* , 296(2):374-82.

Lothian B, Grey V, Kimoff RJ, Lands LC. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. *Chest.* 2000 Mar;117(3):914-6.

Lupton, J. R. (2004). Glutathione Metabolism and its implications for health. *J Nutr* , 134(3):489-92.

Makino, N., Maeda, T., Oyama, J., Sasaki, M., Higuchi, Y., Mimori, K., et al. (2011). Antioxidant therapy attenuates myocardial telomerase activity reduction in superoxide dismutase-deficient mice. *J Mol Cell Cardiol* , 50(4):670-7.

Markovic, J., Garcia-Gimenez, J. L., Gimeno, A., Vina, J., & Pallardo, F. V. (2010). Role of glutathione in cell nucleus. *Free Radiac Res* , 44(7):721-33.

Metcalfe, N. B., & Alonso-Avarez, C. (2010). THE ECOLOGY OF ANTIOXIDANTS &

OXIDATIVE STRESS IN ANIMALS: Oxidative stress as a life-history constraint: the role of reactive oxygen species in shaping phenotypes from conception to death. *Functional Ecology* , 24(5):984-996.

Micke P, Beeh KM, Buhl R. Effects of long-term supplementation with whey proteins on plasma glutathione levels of HIV-infected patients. *Eur J Nutr*. 2002 Feb;41(1):12-8.

Micke P, Beeh KM, Schlaak JF, Buhl R. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. *Eur J Clin Invest*. 2001 Feb;31(2):171-8.

Ozsarlak-Sozer, G., Kerry, Z., Gokce, G., Oran, I., & Topcu, Z. (2011). Oxidative stress in relation to telomere length maintenance in vascular smooth muscle cells following balloon angioplasty. *J Physiol Biochem* , 6(1):35-42.

Pallardo, F. V., Markovic, J., Garcia, J. L., & Vina, J. (2009). Role of nuclear glutathione as a key regulator of cell proliferation. *Mol Aspects Med* , 30(1-2):77-85.

Rodriguez-Brenes, I. A., & Peskin, C. S. (2010). Quantitative theory of telomere length regulation and cellular senescence. *Proceedings of the National Academy of Sciences of the United States of America* , 107 (12):5387-5392.

Rufer, N., Dragowska, W., Thornbury, G., Roosneck, & Lansdorp, P. M. (1998). Telomere length dynamics in human lymphocyte subpopulations measured by flow cytometry. *Nat Biotechnol* , 16 (8):743-747.

Shen, M., Haggblom, C., Vogt, M., Hunter, T., & Lu, K. P. (1997). Characterization and Cell Cycle Regulation of the Related Human Telomeric Proteins Pin2 and TRF1 Suggest a Role in Mitosis. *Proceedings of the National Academy of Sciences of the United States of America* , 94(25):13618-13623.

Vina J, Lloret A, Orti R, Alonso D. Molecular bases of the treatment of Alzheimer's disease with antioxidants: prevention of oxidative stress. *Mol Aspects Med*. 2004 Feb;25(1-2):117-23.

Wang, Y., Erdmann, N., Gianno, R. J., Wu, J., Gomez, M., Li, Y., et al. (2005). An Increase in Telomere Sister Chromatid Exchange in Murine Embryonic Stem

Cells Possessing Critically Shortened Telomeres. *Proceedings of the National Academy of Sciences of the United States of America* , 102(29):10256-10260.

Watfa, G., Dragonas, C., Brosche, T., Dittrich, R., CSieber, C., Alecu, C., et al. (2011). Study of telomere length and different markers of oxidative stress in patients with parkinson's disease. *J Nutr Health Aging* , 15(4):277-81.

Xi, H., Li, C., Ren, F., Zhang, H., & Zhang, L. (2013). Telomere, aging and age-related diseases. *Aging Clin Exp Res* , 25(2):139-46.

Xu, Z., Duc, K. D., Holcman, D., & Teixeira, M. T. (2013). The length of the shortest telomere as the major determinant of the onset of replicative senescence. . *Genetics* , 194 (4):847-57.