The 2nd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/4/20220527

Human Senescence: Fundamental Causes, Telomere Shortening and Consequences

Chengxiang Huang

WLSA Shanghai Academy,Zhengxi Road, Yangpu District, Shanghai, 200243

Corresponding author: carpehuang@st.btbu.edu.cn

Abstract. Senescence, also known as biological aging, is the gradual deterioration of functional characteristics in living organisms. Human civilization has spent tremendous efforts dealing with senescences in the past centuries. In the process of senescence, cellular and genetic-based materials face several variations, and they can be varied beneficially by preventing cancer cell development, such as tumor cells. However, it surely will result in several problems due to cellular senescence. Moreover, factors contributing to human senescence will be elaborated in the following review paper. Telomere will be one factor that plays an essential role in growing old. Due to its unique characteristic of shortening, the ability to repair after the replication will be heavily reduced. Thus, this review intended to illustrate the overall process of human senescence, which involves fundamental causes of senescence, telomere shortening, and its consequences.

Keywords: Senescence, Reactive oxygen species, Telomere, Type-2 diabetes

1. Introduction

Cellular senescence is a cell state implicated in various physiological processes and a broad spectrum of age-related diseases.[1] Senescence already has a long history in the entire human civilization. In ancient China (BC 259), one of the most extraordinary Chinese emperors, QinShi Huang, who united China from several small countries, had been researching the drugs that could help him live eternally. It can also be known as the elixir of life. However, thanks to the development of biological and chemical techniques in the modern world, human is starting to have a positive and objective way of viewing the fact of senescence. Modern biologists viewed senescence as a natural "rule" that increases organism death rate and decreases their fecundity rate, which formed the natural life cycle.[2] Recently, senescence is the damage caused by external and internal factors.[1] Thus, humans have studied the phenomenon of senescence for thousands of years; it used to be seen as a problem because it ultimately results in death and cancers. By contrast, it may also induce specific beneficial effects on humans, which ultimately help human beings to resist certain cancers, such as tumor cells.[3]

Although the cellular process seems natural, it can be interpreted at a genetic level. Primarily, the oncogenic gene activation and other factors which cause the DNA damage will ultimately cause reactive oxygen species (ROS).[4] Since the production of ROS becomes more frequent, which also causes the imbalance of ROS in cells. Those free radicals will result in oxidative stress and become an essential key in senescence formation. Additionally, telomere shortening, or dysfunction, is another factor in cellular senescence. Telomere is the specific DNA–protein structures found at both ends of

DOI: 10.54254/2753-8818/4/20220527

each chromosome that protect the genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion.[5] The telomere's length would be proportional to its ability. However, the telomere length decreases rapidly due to the DNA damage and repeating process in cell division. Therefore, it can also be a crucial cellular senescence factor. Besides those causes, the consequences of senescence will also be crucial, the fact that senescence will indeed cause disability of the immune system, slow rate of cellular reprogramming, and its effect on diabetes as well.

In this assay, the fundamental causes of senescence will be well elaborated. In addition, the telomere shortening effect will be mainly focused on. Especially, recent advances in telomere study will be introduced. Last but not least, the consequences of senescence and aging-related diseases will be discussed to deepen the understanding of senescence.

2. Fundamental causes of senescence

2.1. Reactive oxygen species

Reactive Oxygen Species (ROS) is a type of molecule that contains oxygen and efficiently reacts with others due to its existence of unpaired electrons such as superoxide anion.[6] Those oxygen species would be generated in the human body under two distinctive methods, the first method is to use NADPH oxidase level at the plasma membrane level, and another is to make oxidoreductase reaction in mitochondria.[7] The NADPH oxidase will trigger the translation of electrons through NADPH to oxygens through Nox catalytic subunit to produce ROS.[4] ROS are incredibly reactive in human bodies and can easily bind with other molecules to trigger damage or diseases, such as DNA damage and telomere shortening[6], which will be mentioned in the following articles. Therefore, those ROS, which can also be known as free radicals, can ultimately cause oxidative stress. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and the cell's antioxidant capacity.[8]

For example, oxidative stress can be one potential factor that will cause senescence in several pathways, and it has other factors that also affect human health. For instance, cardiovascular diseases will be a typical one in this case. Generally, this disease has resulted from hypertension, smoking habit, diabetes, and unbalanced diets.[9] However, the actual causes of those cardiovascular diseases (atherosclerosis as an example) are the formation of ROS in macrophages, the form of the cell will be formed, and the lipid will be accumulated in blood vessels. Ultimately, the atherosclerotic plaque will be generated over time. Besides cardiovascular diseases[10], oxidative stress will be an attacker in DNA level, triggering respiratory disease and kidney diseases.[11]

2.2. DNA damage

DNA damage can be defined as any variation in genetic levels which will cause changes in function or coding properties, even disruption of normal function in transcription or replications.[12] DNA damage can result from oxidative stress, as mentioned previously, and it can also be induced by radiation, diet, and environmental chemicals.[13] Antagonistic pleiotropy is one of the most famous aging theories.[14] This theory suggests that activation of DNA damage response may have some ability to prevent cancer cell development. In contrast, senescent cell accumulation and persistent sterile inflammation in old age are believed to be caused by prolonged activation of the DNA damage response. The question that appeared that how those DNA damages result in senescence. DNA damage happens randomly, but how much and what kinds of DNA damage one experiences depends on the expression of genes encoding antioxidant enzymes, genes related to energy and mitochondrial function. Many other factors include histones, methylases, sirtuins, and transcription and replication factors.[15] The cellular reaction to DNA damage determines every facet of how DNA damage could accelerate aging genetically. The unexpected discovery is that DNA damage extensively impacts several cellular metabolic factors associated with aging or the "pillars of aging".[16] This shows that a variety of cellular damage may cause aging but does not manifest itself until several cellular biological processes, such as genomic integrity, proteostasis, and mitochondrial function, are disturbed.[3]

DOI: 10.54254/2753-8818/4/20220527

2.3. Oncogene induced senescence

Oncogenes are genes that have the potential to cause cancer and are highly concentrated in the presence of tumor cells.[17] Additionally, oncogene-induced senescence stimulates the DNA damage response system.[18] The DNA damage checkpoint was triggered, and senescence was caused by overexpression of the proto-oncogene serine/threonine-protein kinasemos, cell division control protein 6 homologs (cdc6), or cyclin E.[3] Senescence is connected with substantial activation of the DSB checkpoint in precancerous lesions. However, the development of carcinoma frequently disrupts this correlation, suggesting that senescence, like apoptosis, may act as a barrier to tumor growth.

3. Telomere shortening

Telomeres are the specific DNA-protein structures found at both ends of each chromosome that protect the genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion.[5] Due to its unique role in repairing and replicating DNAs, its function could specifically relate to human ageing or senescence.[5] Majorly, there is one way that can trigger the shortening effect, which is oxidative stress.

3.1. Telomere shortening

The telomere's ability at the genetic level is due to its lengths at each end of the chromosomes, which specifically correlate positively with the cells' life span.[5] Thus, as the telomere's length got deduced by external factors, the cell's host did experience the little process of senescence.[19] Generally, a telomere will reduce its length automatically due to an increase in age. However, several factors can also trigger this effect of shortening. For instance, oxidative stress can be one critical factor in this situation.[19]

It has been mentioned in the previous articles that oxidative stress will be caused by the unbalanced of free radicals at the cellular level, which causes this potentially threatening stress.[6] There is empirical evidence that shows that oxidative stress can accelerate the process of shortening in the telomere.[20]

The telomere responds differently to oxidative stress at the genetic level than DNA. For the general DNA double helix strains, when they receive DNA damage (oxidative stress), there will be a transient DNA damage response which will trigger DNA damage repair after receiving those damages.[19] In other words, it is inconsequential in senescence establishment. However, it will be partially opposite in the telomere part. When telomere receives oxidative stress-based DNA damage, there will be no repair process. Instead of transient DNA damage signaling, it automatically turned into persistent DNA damage signaling, which is likely to cause cellular senescence and might even cause inflammation and fibrosis.[21]

It can be separated into two cases at the molecular or cellular level.[22] For proliferating tissues, the telomeres got shortened in every cellular division, which can be proof that as time passes, people tend to experience the process of aging more significantly. For other kinds of tissues, post-mitotic tissues (non-proliferating tissues), such as neurons or cardiomyocytes, telomere dysfunction can be caused by telomeres that have irreversible DNA damage. The ongoing DDR activation maintains both times a senescent phenotype with stopped proliferation and activated senescence-associated secretory phenotype.[19]

3.2. Recent advances in telomere study

Since telomere shortening has become one of the significant factors in human senescence, preventing or reversing this process will be the focus of those field scientists.[23] Recently, scientists discovered that an enzyme called telomerase can prevent telomere shortening, ribonucleoprotein that attaches a species-specific telomere repeat sequence to the 3' end of telomeres is also known as a terminal transferase.[24] Telomerase is a reverse transcriptase that functions in combination with telomerase RNA. Telomerase utilizes deoxynucleoside 5'-triphosphates and the 3'-terminus of telomeres as substrates in its reaction (*in vitro* tests it is DNA-oligonucleotide containing the sequence corresponding to telomeric repeats of chromosomes). Using a fixed section of unique telomerase RNA as a template for telomere extension distinguishes telomerase from other RNA-dependent DNA polymerases.[25] In

DOI: 10.54254/2753-8818/4/20220527

addition to interacting with telomeres at this template area, telomerase RNA also does so at what is known as the "anchor site".[26] Telomerase can add many telomeric repeats with a single event of oligonucleotide substrate attachment.[24]

4. Consequences of cellular senescence

Senescence is a double-edged sword that may be employed positively and negatively. Nonetheless, it represents a possible strategy for preventing malignant transformation in a cell. However, senescence can also accelerate cancer development by changing the cellular microenvironment via a secretory phenotype associated with senescence. The aging immune system, namely its influence on lymphocyte formation and function changes, increases the likelihood of latent viral reactivation in older persons.[27]

4.1. TYPE-2 diabetes

It has been suggested that pancreatic cell senescence leads to type 2 diabetes. This may be a direct method by which senescence contributes to diabetes, given that the loss of cell function and mass is a characteristic of type 2 diabetes development.[28]

For the normal pancreatic, it was fulfilled with pancreatic beta cells, and beta cells are pancreatic cells that manufacture and release insulin to control blood glucose levels. Continuously, as external factors cause the formation of senescent beta cells, there will be more pressure that acts on the normal pancreatic beta cells, which is due to the slower rate of producing insulin for regulating blood glucose levels (Senescent beta cells will have a slower rate in proliferating and producing insulins). Therefore, it will ultimately form diabetes due to this imbalance in blood glucose levels, and these kinds of diabetes are also known as type 2 diabetes.[29]

4.2. Senolysis

Senolysis is a class of small molecules under basic research to determine if they can selectively induce the death of senescent cells and improve human health.[30] Basically, by using these techniques, the senescent beta cells could convert into normal or healthy beta cells, which will alternatively increase the proliferating rate and insulin sensitivity. However, this technique is still theoretical, and more research should be done in this field.

5. Conclusion

Overall, the problem of human senescence has been researched by worldwide scientists, and those various causes of senescence will be ultimately solved in the near future. However, solving the problem of senescences may even enlarge the wealth gap in every capitalism-based society. Due to the additional lifetime of using the specific techniques to solve human senescences, the upper classes probably face less risk of cancers, which ultimately have a longer lifetime. Therefore, the number of those classes will dominate the entire society in any region, which leads to the problem of a lack of working labor. Thus, humanity will no longer be sustainable. As a result, more research should be done to prevent and understand senescences, resulting in tangible help soon.

References

[1] V. Gorgoulis, P.D. Adams, A. Alimonti, D.C. Bennett, O. Bischof, C. Bishop, J. Campisi, M. Collado, K. Evangelou, G. Ferbeyre, J. Gil, E. Hara, V. Krizhanovsky, D. Jurk, A.B. Maier, M. Narita, L. Niedernhofer, J.F. Passos, P.D. Robbins, C.A. Schmitt, J. Sedivy, K. Vougas, T. von Zglinicki, D. Zhou, M. Serrano, and M. Demaria, Cell 179, 813–827 (2019).
[2] T.B. Kirkwood, Nature 270, 301–304 (1977).
[3] S. Zeng, W.H. Shen, and L. Liu, Cancer Transl. Med. 4, 70–74 (2018).
[4] M. Schieber and N.S. Chandel, Curr. Biol. 24, R453–R462 (2014).
[5] M.A. Shammas, Curr. Opin. Clin. Nutr. Metab. Care 14, 28–34 (2011).
[6] C. Migdal and M. Serres, Med. Sci. (Paris) 27, 405–412 (2011).
[7] A. Panday, M.K. Sahoo, D. Osorio, and S. Batra, Cell Mol. Immunol. 12, 5–23 (2015).

[8] J.-C. Preiser, J. Parenter. Enteral. Nutr. 36, 147–154 (2012).
[9] G. Pizzino, N. Irrera, M. Cucinotta, G. Pallio, F. Mannino, V. Arcoraci, F. Squadrito, D. Altavilla, and A. Bitto, Oxid. Med. Cell. Longev. 2017, 8416763 (2017).
[10] T. Senoner and W. Dichtl, Nutrients 11, E2090 (2019).
[11] M. Gyurászová, R. Gurecká, J. Bábíčková, and Ľ. Tóthová, Oxid. Med. Cell Longev. 2020, 5478708 (2020).
[12] S.P. Jackson and J. Bartek, Nature 461, 1071–1078 (2009).
[13] P. Jeggo and M. Löbrich, Radiat. Prot. Dosimetry 122, 124–127 (2006).
[14] J. Mitteldorf, Biochemistry (Mosc) 84, 1458–1468 (2019).
[15] H. Jing and H. Lin, Chem. Rev. 115, 2350–2375 (2015).
[16] S. Maynard, E.F. Fang, M. Scheibye-Knudsen, D.L. Croteau, and V.A. Bohr, Cold Spring Harb Perspect. Med. 5, a025130 (2015).
[17] C. Chandeck and W.J. Mooi, Adv. Anat. Pathol. 17, 42–48 (2010).
[18] T. Ishida, M. Ishida, S. Tashiro, and Y. Takeishi, Biol. Pharm. Bull. 42, 531–537 (2019).
[19] F. Rossiello, D. Jurk, J.F. Passos, and F. d'Adda di Fagagna, Nat. Cell Biol. 24, 135–147 (2022).
[20] J. Liu, S. Chen, S. Biswas, N. Nagrani, Y. Chu, S. Chakrabarti, and B. Feng, Physiol. Rep. 8, e14331 (2020).
[21] N.C. Allen, N.S. Reyes, J.Y. Lee, and T. Peng, Front. Cell Dev. Biol. 10, 932723 (2022).
[22] R. Anderson, A. Lagnado, D. Maggiorani, A. Walaszczyk, E. Dookun, J. Chapman, J. Birch, H. Salmonowicz, M. Ogrodnik, D. Jurk, C. Proctor, C. Correia-Melo, S. Victorelli, E. Fielder, R. Berlinguer-Palmini, A. Owens, L.C. Greaves, K.L. Kolsky, A. Parini, V. Douin-Echinard, N.K. LeBrasseur, H.M. Arthur, S. Tual-Chalot, M.J. Schafer, C.M. Roos, J.D. Miller, N. Robertson, J. Mann, P.D. Adams, T. Tchkonia, J.L. Kirkland, J. Mialet-Perez, G.D. Richardson, and J.F. Passos, EMBO J. 38, e100492 (2019).
[23] E. Fathi, H.N. Charoudeh, Z. Sanaat, and R. Farahzadi, Stem Cell Investig. 6, 7 (2019).
[24] M.I. Zvereva, D.M. Shcherbakova, and O.A. Dontsova, Biochemistry (Mosc) 75, 1563–1583 (2010).
[25] P.P. Schrumpfová and J. Fajkus, Biomolecules 10, E1425 (2020).
[26] N.F. Lue, J. Biol. Chem. 280, 26586–26591 (2005).
[27] R. Kumari and P. Jat, Front. Cell Dev. Biol. 9, 645593 (2021).
[28] T. Murakami, N. Inagaki, and H. Kondoh, Front. Endocrinol. 13, 869414 (2022).
[29] M.Y. Donath, J.A. Ehses, K. Maedler, D.M. Schumann, H. Ellingsgaard, E. Eppler, and M. Reinecke, Diabetes 54, S108–S113 (2005).
[30] B.G. Childs, M. Durik, D.J. Baker, and J.M. van Deursen, Nat. Med. 21, 1424–1435 (2015).