ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

ASSOCIATION OF TELOMERE WITH AGEING THROUGH CELLULAR SENESCENCE AND MITOCHONDRIAL MALFUNCTION

Dr. Ranjana Kudesia*Dr. Deepshikha Saxena**
Department of Zoology*Institute of Education & Research**
*Himalayan University, Ita Nagar (Arunachal Pradesh)
**Mangalayatan University, Aligarh, (Uttar Pradesh)

Abstract
Marked by a progressive decline in the function of tissues and organs that ultimately results in death,Aging is a biological conditionTelomeres, are repetitive DNA sequences necessary for cell fate and aging. Telomeres shorten when cells mature, resulting in cellular senescence and mitochondrial dysfunction.. "Cellular senescence and mitochondrial malfunction" will then result in organ or tissue degeneration and dysfunction, as well as a variety of somatic ageing mechanisms. We summarized the relationship between cell senescence, mitochondrial dysfunction, and aging in this paper.

1. INTRODUCTION

Mammalian telomeres consist of "TTAGGG" repeats in humans and mice ranging from 5 kb to 100 kb respectively and are associated with shelterin, a protein complex (de Lange 2005).However, due to the "mid-replication issue" and telomere end processing, telomeres gradually shorten with cell division (Wu et al. 2012). Shelterin can lose its binding site when telomeres exceed a critical length and telomeric DNA is unable to form a protective secondary structure. While its biological mechanisms remain largely unclear, the primary hallmark of ageing has been telomere attrition ("Lopez-Otin et al. 2013 and McHugh and Gil 2018"). "Cellular senescence and mitochondrial dysfunction" are two other major ageing hallmarks and can also be mediated by telomere shortening ("Sahin et al. 2011"). In this analysis, we start by explaining the structure and function of the telomerase.

2. TELOMERE STRUCTURE AND FUNCTION

Barbara McClintock and Herman Muller first hypothesised on advanced telomere structures that can protect the normal ends of linear chromosomes from the repair of aberrant DNA (McClintock 1941) as well as instability of genome (Lazzerini-Denchi and Sfeir 2016).

Telomeric DNA in mammals consists of tandem repeats of TTAGGG which end in single-stranded G-rich thirty overhangs, recognized as G-overhangs (Moyzis et al. 1988). "The G-overhang will invade the double-stranded telomeric DNA that forms a lariat-like structure called the t-loop, observed by electron microscopy as well as stochastic optical reconstruction microscopy in functional telomeres (Doksani et al. 2013 and Griffith et al. 1999). Telomeres can fold into a closed structure by creating t-loops to shield the chromosome ends from being detected by the DNA damage repair machinery as DNA double-strand breaks (Morgan et al. 2018). Telomeric DNA, called G-quadruplexes (Schaffitzel et al. 2001), is also likely to fold into nocanonical secondary structures and plays an important role in capping telomeres to maintain chromosomal integrity and inhibit DNA damage signals in telomeres (Ray et al. 2014 and Smith et al. 2011). In addition, the structure of telomeric G-quadruplexes has been shown to limit telomer extension by affecting telomerase function (Oganesian et al. 2006). In promoters and transcription start sites, G-quadruplexes structures are also found (Bedrat et al. 2016 and Chambers et al. 2015)." Therefore, DNA replication,translationand transcription have regulatory roles ("Hansel-Hertsch et al. 2017 and Rhodes and Lipps 2015").

Telomerase is a "ribonucleoprotein complex made up of the catalytic core of telomerase reverse transcriptase and telomerase RNA".Telomerase prolongs telomeres by tethering to the 3' end of DNA, using the telomerase reverse transcriptase's catalyzed reverse transcription as a guide.("Jiang et al. 2018 and Wu et al. 2017"). "RNA polymerase II synthesizes noncoding telomeric repeat RNA by converting subtelomeric DNA to telomeric repeat sequences" (Schoeftner and Blasco 2008). "A telomeric repeat containing RNA has been identified as a component of telomeric heterochromatin, which is thought to act as a molecular scaffold for multiple protein enzymes that perform a variety of critical chromosome-end functions" (Azzalin and Lingner 2015) and contributes significantly to telomeric integrity ("Chu et al. 2017 and Montero et al. 2016"). Further research to investigate the association between telomeric repeat-containing RNA and telomerase should therefore be performed. With the exception of this telomeric repeat-containing RNA, R-loops will activate the DNA damage reaction at critically short telomeres (Graf et al. 2017).

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

Telomeres complexes known as shelterin complexes, which are associated with proteins that shield chromosome ends from DNA damage reaction and keep genome stability. (Blackburn et al. 2015).“Shelterin ends with telomeric DNA after recruitment to secure chromosomes. Shelterin binds specifically to telomeric DNA and protects telomeres by affecting the telomeric DNA structure, preventing DNA damage response directly from telomeres and preserving telomeric DNA by modulating telomerase activity (Benarroch-Popivker et al. 2016 and Kibe et al. 2016).”

3. TELOMERE, CELLULAR SENESCENCE AND AGEING

DNA is replicated in a semi-conservative manner. “DNA replication is continuous in the direction of the advancing replication fork for the leading strand, but discontinuous for the lagging strand, which is formed by merging Okazaki fragments. Because DNA polymerase can only continue (but not initiate) a strand, Okazaki fragment formation requires an RNA primer generated by RNA polymerase.” Following the synthesis of Okazaki fragments, the “RNA primers” are removed and the internal gaps are filled with DNA using DNA polymerase I. The Okazaki fragments are subsequently joined using ligase. Due to DNA replication the relomere shortens.. This is Watson's 1972 "end-replication problem." (“1973; Olovnikov; Sugino et al., 1972; Watson, 1972”). However, inadequate replication is not the primary cause of telomere shortening. Following replication at leading-end telomeres, the G overhang is produced by the excision of five primary ends, which contributes significantly to telomere attrition (“Wu et al. 2012). Except for the end replication issue and resection of the telomere 5' end, telomere attrition rates are associated with a variety of other variables, such as reactive oxygen species, that may accelerate telomere shortening (Herbert et al. 2008”). Olovnikov (1973) related the Hayflick limit to telomere replication and indicated that telomere duration could decide the possible number of rounds of cell division (Olovnikov 1973). “In 1986, Cooke and Smith specifically related telomeres to cell ageing when they compared telomere lengths in different tissues (Cooke and Smith 1986). Over the next few years, researchers have found that because telomerase extends the telomeres, the replicative ability of human cells increases. These studies demonstrated that progressive shortening of telomeres is indeed the primary factor contributing to senescence (Allsopp et al. 1992 and Harley et al. 1992).”Telomeres are known as the "molecular clocks" of cells (“Muezzinler et al. 2013”). Telomeres gradually lose their protective structure and proteins, finally causing replicative senescence via DNA damage response mechanisms (Morgan et al. 2018). In somatic cells lacking telomerase production, telomeres shorten with each replication cycle, and when crucial telomere shortening occurs, short telomeres are identified as double-strand DNA breaks (Arnoult and Karlseder 2015). The DNA damage response is triggered by double-strand breaks, which triggers a signaling cascade that culminates in the activation of the ATM kinase p533 (“Roake and Artandi 2017 and Wang et al. 2011”). In most malignancies, the tumor suppressor P53 is tightly regulated and dormant, but it becomes active in senescent cells due to a posttranslational change (Itahana et al. 2001). P21 was the first to be found, and it inhibits Cdk2 through inhibiting pRb phosphorylation. Hypophosphorylated Rb interacts to transcription factors, particularly E2Fs, which are involved in cell growth, and the cell cycle is stopped at the G1 phase.(“Beausejour et al. 2003; Harper et al. 1993; Shay et al. 1991 and Xiong et al. 1993”). Telomerase, which solves the endreplication problem, is essential for telomere length maintenance in these cells (“Borah et al. 2015; Kim et al. 1994 and Morin 1989”). Shelterin is a compound that attracts telomerase to telomeres and allows for telomere extension.

Numerous studies have established a possible link between telomere length and aging. It would prolong the lives of mice by restoring the function or duration of telomeres, and telomerase gene therapy might be used to treat premature aging and delay physical aging in animals (“Armanios et al. 2009; Bernardes de Jesus et al. 2012; Derevyanko et al. 2017 and Steenstrup et al. 2017”). Senescence induces tiredness and a reduction in stem cell function, impairing tissue breakdown. (Bernet et al. 2014). Senescent cells, however, can force stem cells to re-enter the cell cycle via the secretory phenotype associated with senescence, which accelerates stem cell fatigue (“Cosgrove et al. 2014 and Sousa-Victor et al. 2014”).

Senescence has the potential to alter the optimal functioning of stem cells non-autonomously via the senescence-associated secretory phenotype, in addition to impacting stem cells by causing a protracted growth stop. (“Brack et al. 2007; Jang et al. 2011 and Pricola et al. 2009”). “Senescent cells secrete hundreds of factors that manifest drastic changes in their secretome called the senescence-associated secretory phenotype which is enriched with proinflammatory cytokines, growth factors of chemokine and proteases (Coppe et al. 2010 and Kuilman and Peeper 2009). Emerging research using genetic systems or drugs that remove senescent cells suggest that senescent cell clearance attenuates inflammation and creates a pro-regenerative environment (Jeon et al. 2017). In addition, several studies have shown that exposure to a young systemic environment markedly increased the regenerative capacity of old stem cells (Brack et al. 2007 and Conboy et al. 2005).”Senescent cells are thought to have a paracrine activity, in which they release IL-1b, TGFbeta, and specific chemokine ligands, promoting the degeneration of age-related tissue.(“Acosta et al. 2013 and Nelson et al. 2012”).

Studies have shown that senescent cell clearance decreases levels of chronic inflammatory markers, IL-6 and IL-1b, in the elderly, indicating that the senescence-associated secretory phenotype is partly behind chronic

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

inflammation, often referred to as inflammatory inflammation ("Baker et al. 2016 and Jeon et al. 2017"). The secretory phenotype associated with senescence will recruit immune cells to kill senescent cells, called immunosenescence (Nikolich-Zugich 2018). Hematopoietic stem cell dysfunction can result in a decline in immune system function (Sahin et al. 2011). The increase of senescent cells throughout aging may be explained by senescent cells secreting inflammatory substances in an autocrine or paracrine way to facilitate senescence and a fall in their clearance.(Sharpless 2017).

4. TELOMERE, MITOCHONDRIA DYSFUNCTION AND AGING

Telomere shortening and mitochondrial dysfunction have long been recognized as critical initiators of natural ageing. ((Fang et al. 2016). P53 and DDR pathways are triggered when "DNA damage occurs due to telomere dysfunction, which in turn suppresses peroxisome proliferator-activated receptor gamma co-activator 1 alpha/beta, contributing to mitochondrial dysfunction" (Dabrowska et al. 2015). In addition, research has shown that overexpression of (PGC-1 alpha) peroxisome proliferator-activated gamma co-activator 1 alpha receptor can reverse ageing muscle at the molecular level to younger muscle and play an important role in longevity ("Garcia et al. 2018"). "The NAD+-SIRT1-PGC-1 axis is another prominent pathway connecting telomere attrition to mitochondrial dysfunction. Short telomeres are sensed in this axis as doubled-strand breaks by nicotinamide adenine dinucleotide (NAD+)-dependent PARP1, which can trigger signalling for DNA repair, a process involving NAD+ consumption. PARP1 hyperactivation results in consumption of NAD+, thus restricting the activity of the NAD+-dependent deacetyase sirtuin 1 (SIRT1) (Fang 2014). SIRT1 has been shown to increase mitochondrial function and biogenesis through the PGC-1 alpha transcription factor, and loss of SIRT1 activity could contribute to mitochondrial dysfunction, particularly in muscle dysfunction (Fang 2014). By increasing mitochondrial biogenesis, telomere shortening can also have an effect on the ageing process as activation of ATM due to DNA damage triggers AKT and the mechanistic target of rapamycin complex 1, resulting in mitochondrial biogenesis based on PGC-1beta and ROS generation (Correia-Melo et al. 2016)."Thus, either an excess or a deficiency of mitochondrial synthesis can result in mitochondrial malfunction..(Kauppila et al. 2017).

Mitochondrial dysfunction results from disruption of metabolic balance, which includes gluconeogenesis, fatty acid metabolism, and -oxidation. Cell dysfunction can be caused by metabolic imbalances, which can lead to cellular senescence via a variety of ways.. ("Sui et al. 2016 and Wiley and Campisi 2016").Excessive reactive oxygen species formation as a result of telomere shortening has been proven to stabilize the DNA damage response and keep cells alive..(Correia-Melo et al. 2016). "In defective mitochondria, decreased ATP production increases the AMP-to-ATP ratio that promotes cellular senescence by stimulating AMPK, a key mediator of cellular metabolism" (Mihaylova and Shaw 2011).

This research established that compromised mitochondria decreased "NAD+/NADH" ratios, resulting in senescence associated with mitochondrial dysfunction via activation of "AMPK, which induces p53-dependent senescence, and that mitochondrial dysfunction induces ageing phenotypes via distinct senescence-associated secretory phenotype components such as CCL27, IL-10, HMB1, and TNF alpha", all of which affect survivability.("Davalos et al. 2013; Frankel et al. 2013 and Wiley et al. 2016"). Additionally, the mitochondrial respiratory chain is required for the differentiation of foetal hematopoietic stem cells into progenitor cells and adult hematopoietic stem cell quiescence. Respiratory dysfunction caused by mitochondrial dysfunction would also impair hematopoietic stem cell differentiation, resulting in the loss of quiescence.(Anso et al. 2017). ("Prolla and Denu 2014; Son et al. 2016; Verdin 2015 and Zhang et al. 2016"). Studies have revealed serious episodes of telomere attrition causing severe inflammation predominantly through mitochondrial oxidative stress hyperactivation of the inflammasome.NLRP3 (Kang et al. 2018).

5. CONCLUSION

Telomere shortening in cells appears to be a cause of human aging. Telomere shape variation, shelterin complexes, and tight telomeric chromatin all play a role in keeping chromosomes from degrading with age. "Telomere shortening" is being related to cellular and organismal aging. Finally, determining how cellular senescence and mitochondria cause aging is difficult...

REFERENCES

[1]. Acosta, J. C., Banito, A., Wuestefeld, T., Georgilis, A., Janich, P., Morton, J. P., Gil, J. (2013). A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nature Cell Biology, 15(8), 978–990.

[2]. Alder, J. K., Barkauskas, C. E., Limjunyawong, N., Stanley, S. E., Kembou, F., Tuder, R. M., Armanios, M. (2015). Telomere dysfunction causes alveolar stem cell failure. Proceedings of the National Academy of Sciences of the United States of America, 112(16), 5099–5104.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

[3]. Ansó, E., Weinberg, S. E., Diebold, L. P., Thompson, B. J., Malinge, S., Schumacker, P. T., Chandel, N. S. (2017). The mitochondrial respiratory chain is essential for haematopoietic stem cell function. Nature Cell Biology, 19(6), 614–625.
[4]. Armanios, M., Alder, J. K., Parry, E. M., Karim, B., Strong, M. A., & Greider, C. W. (2009). Short telomeres are sufficient to cause the degenerative defects associated with aging. The American Journal of Human Genetics, 85(6), 823–832.
[5]. Arnoult, N., & Karlseder, J. (2015). Complex interactions between the DNA-damage response and mammalian telomeres. Nature Structural & Molecular Biology, 22(11), 859–866.
[6]. Azzalin, C. M., & Lingner, J. (2015). Telomere functions grounding on TERRA firma. Trends in Cell Biology, 25(1), 29–36.
[7]. Baker, D. J., Childs, B. G., Durik, M., Wijers, M. E., Sieben, C. J., Zhong, J., … van Deursen, J. M. (2016). Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. Nature, 530(7589), 184–189.
[8]. Bandaria, J. N., Qin, P., Berk, V., Chu, S., & Yildiz, A. (2016). Shelterin protects chromosome ends by compacting telomeric chromatin. Cell, 164(4), 735–746.
[9]. Bedrat, A., Lacroix, L., & Mergny, J.-L. (2016). Re-evaluation of G-quadruplex propensity with G4Hunter. Nucleic Acids Research, 44(4), 1746–1759.
[10]. Benarroch-Popivker, D., Pisano, S., Mendez-Bermudez, A., Lototska, L., Kaur, P., Bauwens, S., Giraud-Panis, M.-J. (2016). TRF2-mediated control of telomere DNA topology as a mechanism for chromosome-end protection. Molecular Cell, 61(2), 274–286.
[11]. Bernardes de Jesus, B., Vera, E., Schneeberger, K., Tejera, A. M., Ayuso, E., Bosch, F., & Blasco, M. A. (2012). Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer: TERT alone extends lifespan of adult/old mice. EMBO Molecular Medicine, 4(8), 691–704.
[12]. Bernet, J. D., Doles, J. D., Hall, J. K., Kelly Tanaka, K., Carter, T. A., & Olwin, B. B. (2014). p38 MAPK signaling underlies a cell-autonomous loss of stem cell self-renewal in skeletal muscle of aged mice. Nature Medicine, 20(3), 265–271.
[13]. Blackburn, E. H., Epel, E. S., & Lin, J. (2015). Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science (New York, N.Y.), 350(6265), 1193–1198.
[14]. Borah, S., Xi, L., Zaug, A. J., Powell, N. M., Dancik, G. M., Cohen, S. B., Cech, T. R. (2015). Cancer. TERT promoter mutations and telomerase reactivation in urothelial cancer. Science (New York, N.Y.), 347(6225), 1006–1010.
[15]. Chambers, V. S., Marsico, G., Boutell, J. M., Di Antonio, M., Smith, G. P., & Balasubramanian, S. (2015). High-throughput sequencing of DNA G-quadruplex structures in the human genome. Nature Biotechnology, 33(8), 877–881.
[16]. Chandel, N. S., Jasper, H., Ho, T. T., & Passegué, E. (2016). Metabolic regulation of stem cell function in tissue homeostasis and organismal ageing. Nature Cell Biology, 18(8), 823–832.
[17]. Childs, B. G., Durik, M., Baker, D. J., & van Deursen, J. M. (2015). Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nature Medicine, 21(12), 1424–1435.
[18]. Chu, H.-P., Cifuentes-Rojas, C., Kesner, B., Aeby, E., Lee, H.-G., Wei, C., Lee, J. T. (2017). TERRA RNA antagonizes ATRX and protects telomeres. Cell, 170(1), 86-101.e16.
[19]. Coppé, J.-P., Desprez, P.-Y., Krtolica, A., & Campisi, J. (2010). The senescence-associated secretory phenotype: the dark side of tumor suppression. Annual Review of Pathology, 5(1), 99–118.
[20]. Correia-Melo, C., Marques, F. D. M., Anderson, R., Hewitt, G., Hewitt, R., Cole, J., Passos, J. F. (2016). Mitochondria are required for pro-ageing features of the senescent phenotype. The EMBO Journal, 35(7), 724–742.
[21]. Cosgrove, B. D., Gilbert, P. M., Porpiglia, E., Mourkioti, F., Lee, S. P., Corbel, S. Y., Blau, H. M. (2014). Rejuvenation of the muscle stem cell population restores strength to injured aged muscles. Nature Medicine, 20(3), 255–264.
[22]. Dabrowska, A., Venero, J. L., Iwasawa, R., Hankir, M.-K., Rahman, S., Boobis, A., & Hajji, N. (2015). PGC-1α controls mitochondrial biogenesis and dynamics in lead-induced neurotoxicity. Aging, 7(9), 629–647.
[23]. Davalos, A. R., Kawahara, M., Malhotra, G. K., Schaum, N., Huang, J., Ved, U., Campisi, J. (2013). Pre-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. The Journal of Cell Biology, 201(4), 613–629.
[24]. Deng, Z., Norseen, J., Wiedmer, A., Riethman, H., & Lieberman, P. M. (2009). TERRA RNA binding to TRF2 facilitates heterochromatin formation and ORC recruitment at telomeres. Molecular Cell, 35(4), 403–413.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

[25]. Derevyanko, A., Whittemore, K., Schneider, R. P., Jiménez, V., Bosch, F., & Blasco, M. A. (2017). Gene therapy with the TRF1 telomere gene rescues decreased TRF1 levels with aging and prolongs mouse health span. Aging Cell, 16(6), 1353–1368.

[26]. Doksani, Y., Wu, J. Y., de Lange, T., & Zhuang, X. (2013). Super-resolution fluorescence imaging of telomeres reveals TRF2-dependent T-loop formation. Cell, 155(2), 345–356.

[27]. Erdel, F., Kratz, K., Willcox, S., Griffith, J. D., Greene, E. C., & de Lange, T. (2017). Telomere recognition and assembly mechanism of mammalian shelterin. Cell Reports, 18(1), 41–53.

[28]. Fang, E. F., Scheibye-Knudsen, M., Brace, L. E., Kassahun, H., SenGupta, T., Nilsen, H., Bohr, V. A. (2014). Defective Mitophagy in XPA via PARP-1 Hyperactivation and NAD+/SIRT1 Reduction. Cell, 157(4), 882–896.

[29]. Fang, E. F., Scheibye-Knudsen, M., Chua, K. F., Mattson, M. P., Croteau, D. L., & Bohr, V. A. (2016). Nuclear DNA damage signalling to mitochondria in ageing. Nature Reviews. Molecular Cell Biology, 17(5), 308–321.

[30]. Frankel, L. K., Sallans, L., Limbach, P. A., & Bricker, T. M. (2013). Oxidized amino acid residues in the vicinity of Q(A) and Pheo(D1) of the photosystem II reaction center: putative generation sites of reducing-side reactive oxygen species. PloS One, 8(2), e58042.

[31]. Garcia, S., Nissanka, N., Mareco, E. A., Rossi, S., Peralta, S., Diaz, F., Moraes, C. T. (2018). Overexpression of PGC-1α in aging muscle enhances a subset of young-like molecular patterns. Aging Cell, 17(2). doi:10.1111/acel.12707

[32]. Gaullier, G., Miron, S., Pisano, S., Buisson, R., Le Bihan, Y.-V., Tellier-Lebègue, C., Le Du, M.-H. (2016). A higher-order entity formed by the flexible assembly of RAP1 with TRF2. Nucleic Acids Research, 44(4), 1962–1976.

[33]. Graf, M., Bonetti, D., Lockhart, A., Serhal, K., Kellner, V., Maicher, A., Luke, B. (2017). Telomere length determines TERRA and R-loop regulation through the cell cycle. Cell, 170(1), 72-85.e14.

[34]. Hänsel-Hertsch, R., Di Antonio, M., & Balasubramanian, S. (2017). DNA G-quadruplexes in the human genome: detection, functions and therapeutic potential. Nature Reviews. Molecular Cell Biology, 18(5), 279–284.

[35]. He, S., & Sharpless, N. E. (2017). Senescence in health and disease. Cell, 169(6), 1000–1011.

[36]. Ito, K., & Suda, T. (2014). Metabolic requirements for the maintenance of self-renewing stem cells. Nature Reviews. Molecular Cell Biology, 15(4), 243–256.

[37]. Jang, Y. C., Sinha, M., Cerletti, M., Dall'Osso, C., & Wagers, A. J. (2011). Skeletal muscle stem cells: effects of aging and metabolism on muscle regenerative function. Cold Spring Harbor Symposia on Quantitative Biology, 76(0), 101–111.

[38]. Jeon, O. H., Kim, C., Laberge, R.-M., Demaria, M., Rathod, S., Vasserot, A. P., Elisseeff, J. H. (2017). Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nature Medicine, 23(6), 775–781.

[39]. Jiang, J., Wang, Y., Sušac, L., Chan, H., Basu, R., Zhou, Z. H., & Feigon, J. (2018). Structure of telomerase with telomeric DNA. Cell, 173(5), 1179-1190.e13.

[40]. Kang, Y., Zhang, H., Zhao, Y., Wang, Y., Wang, W., He, Y., Shi, L. (2018). Telomere dysfunction disturbs macrophage mitochondrial metabolism and the NLRP3 inflammasome through the PGC-1α/TNFAIP3 axis. Cell Reports, 22(13), 3493–3506.

[41]. Kauppila, T. E. S., Kauppila, J. H. K., & Larsson, N.-G. (2017). Mammalian mitochondria and aging: An update. Cell Metabolism, 25(1), 57–71.

[42]. Kibe, T., Zimmermann, M., & de Lange, T. (2016). TPP1 blocks an ATR-mediated resection mechanism at telomeres. Molecular Cell, 61(2), 236–246.

[43]. Lawless, C., Wang, C., Jurk, D., Merz, A., Zglinicki, T. von, & Passos, J. F. (2010). Quantitative assessment of markers for cell senescence. Experimental Gerontology, 45(10), 772–778.

[44]. Lazzerini-Denchi, E., & Sfeir, A. (2016). Stop pulling my strings - what telomeres taught us about the DNA damage response. Nature Reviews. Molecular Cell Biology, 17(6), 364–378.

[45]. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. Cell, 153(6), 1194–1217.

[46]. Maryanovich, M., Zaltsman, Y., Ruggiero, A., Goldman, A., Shachnai, L., Zaidman, S. L., Gross, A. (2015). An MTCH2 pathway repressing mitochondria metabolism regulates haematopoietic stem cell fate. Nature Communications, 6(1), 7901.

[47]. McHugh, D., & Gil, J. (2018). Senescence and aging: Causes, consequences, and therapeutic avenues. The Journal of Cell Biology, 217(1), 65–77.

[48]. Mihaylova, M. M., & Shaw, R. J. (2011). The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nature Cell Biology, 13(9), 1016–1023.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

[49]. Montero, J. J., López de Silanes, I., Graña, O., & Blasco, M. A. (2016). Telomeric RNAs are essential to maintain telomeres. Nature Communications, 7(1), 12534.
[50]. Moravec, M., Wischnewski, H., Bah, A., Hu, Y., Liu, N., Lafranchi, L., Azzalin, C. M. (2016). TERRA promotes telomerase-mediated telomere elongation in Schizosaccharomyces pombe. EMBO Reports, 17(7), 999–1012.
[51]. Morgan, R. G., Donato, A. J., & Walker, A. E. (2018). Telomere uncapping and vascular aging. American Journal of Physiology. Heart and Circulatory Physiology, 315(1), H1–H5.
[52]. Müezzinler, A., Zaineddin, A. K., & Brenner, H. (2013). A systematic review of leukocyte telomere length and age in adults. Ageing Research Reviews, 12(2), 509–519.
[53]. Nelson, G., Wordsworth, J., Wang, C., Jurk, D., Lawless, C., Martin-Ruiz, C., & von Zglinicki, T. (2012). A senescent cell bystander effect: senescence-induced senescence: Senescence induces senescence. Aging Cell, 11(2), 345–349.
[54]. Nikolich-Žugich, J. (2018). The twilight of immunity: emerging concepts in aging of the immune system. Nature Immunology, 19(1), 10–19.
[55]. Pricola, K. L., Kuhn, N. Z., Haleem-Smith, H., Song, Y., & Tuan, R. S. (2009). Interleukin-6 maintains bone marrow-derived mesenchymal stem cell stemness by an ERK1/2-dependent mechanism. Journal of Cellular Biochemistry, 108(3), 577–588.
[56]. Prolla, T. A., & Denu, J. M. (2014). NAD+ deficiency in age-related mitochondrial dysfunction. Cell Metabolism, 19(2), 178–180.
[57]. Ray, S., Bandaria, J. N., Qureshi, M. H., Yildiz, A., & Balci, H. (2014). G-quadruplex formation in telomeres enhances POT1/TPP1 protection against RPA binding. Proceedings of the National Academy of Sciences of the United States of America, 111(8), 2990–2995.
[58]. Redon, S., Reichenbach, P., & Lingner, J. (2010). The non-coding RNA TERRA is a natural ligand and direct inhibitor of human telomerase. Nucleic Acids Research, 38(17), 5797–5806.
[59]. Rhodes, D., & Lipps, H. J. (2015). G-quadruplexes and their regulatory roles in biology. Nucleic Acids Research, 43(18), 8627–8637.
[60]. Roake, C. M., & Artandi, S. E. (2017). Control of cellular aging, tissue function, and cancer by p53 downstream of telomeres. Cold Spring Harbor Perspectives in Medicine, 7(5). doi:10.1101/cshperspect.a026088
[61]. Sahin, E., Colla, S., Liesa, M., Moslehi, J., Müller, F. L., Guo, M., … DePinho, R. A. (2011). Telomere dysfunction induces metabolic and mitochondrial compromise. Nature, 470(7334), 359–365.
[62]. Schoeftner, S., & Blasco, M. A. (2008). Developmentally regulated transcription of mammalian telomeres by DNA-dependent RNA polymerase II. Nature Cell Biology, 10(2), 228–236.
[63]. Smith, J. S., Chen, Q., Yatsunyk, L. A., Nicoludis, J. M., Garcia, M. S., Kranaster, R., Johnson, F. B. (2011). Rudimentary G-quadruplex-based telomere capping in Saccharomyces cerevisiae. Nature Structural & Molecular Biology, 18(4), 478–485.
[64]. Son, M. J., Kwon, Y., Son, T., & Cho, Y. S. (2016). Restoration of mitochondrial NAD+levels delays stem cell senescence and facilitates reprogramming of aged somatic cells: Mitochondrial NAD+rescue stem cells from aging. Stem Cells (Dayton, Ohio), 34(12), 2840–2851.
[65]. Sousa-Victor, P., Gutarra, S., García-Prat, L., Rodriguez-Ubreva, J., Ortet, L., Ruiz-Bonilla, V., Muñoz-Cánoves, P. (2014). Geriatric muscle stem cells switch reversible quiescence into senescence. Nature, 506(7488), 316–321.
[66]. Steenstrup, T., Kark, J. D., Verhulst, S., Thinggaard, M., Hjelmborg, J. V. B., Dalgård, C., Aviv, A. (2017). Telomeres and the natural lifespan limit in humans. Aging, 9(4), 1130–1142.
[67]. Sui, B., Hu, C., & Jin, Y. (2016). Mitochondrial metabolic failure in telomere attrition-provoked aging of bone marrow mesenchymal stem cells. Biogerontology, 17(2), 267–279.
[68]. van Deursen, J. M. (2014). The role of senescent cells in ageing. Nature, 509(7501), 439–446.
[69]. Verdin, E. (2015). NAD^+ in aging, metabolism, and neurodegeneration. Science (New York, N.Y.), 350(6265), 1208–1213.
[70]. Wang, X., Zeng, L., Wang, J., Chau, J. F. L., Lai, K. P., Jia, D., … Li, B. (2011). A positive role for c-Abl in Atm and Atr activation in DNA damage response. Cell Death and Differentiation, 18(1), 5–15.
[71]. Wang, Y., Wang, X., Flores, E. R., Yu, J., & Chang, S. (2016). Dysfunctional telomeres induce p53-dependent and independent apoptosis to compromise cellular proliferation and inhibit tumor formation. Aging Cell, 15(4), 646–660.
[72]. Wiley, C. D., & Campisi, J. (2016). From ancient pathways to aging cells-connecting metabolism and cellular senescence. Cell Metabolism, 23(6), 1013–1021.
[73]. Wiley, C. D., Velarde, M. C., Lecot, P., Liu, S., Sarnoski, E. A., Freund, A., Campisi, J. (2016). Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metabolism, 23(2), 303–314.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

[74]. Wu, P., Takai, H., & de Lange, T. (2012). Telomeric 3' overhangs derive from resection by Exo1 and Apollo and fill-in by POT1b-associated CST. Cell, 150(1), 39–52.

[75]. Wu, R. A., Upton, H. E., Vogan, J. M., & Collins, K. (2017). Telomerase mechanism of telomere synthesis. Annual Review of Biochemistry, 86, 439–460.

[76]. Zhang, H., Ryu, D., Wu, Y., Gariani, K., Wang, X., Luan, P., … Auwerx, J. (2016). NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. Science (New York, N.Y.), 352(6292), 1436–1443.