ACE JOURNAL OF RESEARCH
STUDIES IN
BIOSCIENCES
ACE PUBLICATIONS
www.theacepublications.com

Review Article

# Molecular Physiology of Oxidative Stress in Telomere Shorting and Repair Possibility in Disease: A Review

[1]Methaq J. Al-Jboori, [2]Shaimaa A. Al-Oubaidy and [3]MonaN. Al-Terehi
*[1]Department of biology/College of Science/ Mustansiriyah University /Iraq*
*2Department of human anatomy and histology/ Medical college/ University of Babylon/Iraq*
*[3]Department of Biology/College of science/ University of Babylon/Iraq*

**KEY WORDS:**
Oxidative DNA damage
Telomere shorting
Repair possibility

**Abstract:**
Telomeres have significant focusing researchers in last decades belong to its role in aging and cancer development in mammalian genomes**.** ROS represented as second messengers contributed in several signaling pathways, the current review discussed the impact of oxidative stress (OS) in accelerating telomere length reduction in human, animal and cell line. Different ROS types react with DNA causes more than 100 kinds of oxidative damaged bases, include pyrimidine and purines damages, like single strand breaks and a basic site. Guanine (G) is more common oxidation to generating 8-oxoG, Free radicals can be oxidized Pyrimidine to generate different lesions as well as 5-hydroxy cytosine, thymine glycol (Tg) and 5-hydroxy uracil, the 8-oxoG is the common oxidative injury. DNA oxidative lesions can be repaired by some pathways, In form of 8-oxoG, OGG1 glycosylase discriminate the complement C, to form a basic site by removing the lesion, Which enhanced by XPC, NEIL1 and APE1, further oxidized to other lesions can be occurred like guanidinohydantoin (Gh) and spiroiminodihydantoin (Sp). These destruction distorting hydantoin lesions implicated DNA transcription and replication. OS has significant role in the telomere shortening and human tissues dysfunction, biochemical researches and cell culture. Some mechanisms have been suggested to demonstrate how ROS high level effect on the telomere length homeostasis., belong to the high effective of ROS in cell components, further studies must be implemented to explain if the telomeres legend affected by direct or indirect ROS impacts.

**Corresponding Author:**
Methaq J. Al-Jboori,
Department of biology/College of Science/ Mustansiriyah University /Iraq
sci.muna.najah@uobablon.edu.iq

## INTRODUCTION

In last decades the Telomeres has significant focusing researchers regarding to its role in aging and cancer in mammalian genomes. First, the DNA replication causes lose about 20-50n from chromosome and each cell division. Therefore, development chromosome shortening observed through cell proliferation is found with aging[1]. Several stem cells, Germ cells and some tumor cells protect chromosome shortening by enzyme telomeres level, which added consecutive 5-TTAGGG-3 repeats to chromosome. The telomeres in humans have about 10-15 KB of motif duplex repeats consists of TTAGGG and in a single stranded 3 and that depended as a telomeres substrate[2]. Meanwhile some somatic cells missed telomeres, thus when telomeres become in critical short length, the longer cannot implemented in the chromosome and protection crucial function. Critically short telomeres missed enough region of binding for protein complex, called shelter in, that reform telomeres to a "capped" structure. The telomere cap losing caused exposure chromosome and to destruction and false DNA injury response proteins determination as chromosome parts[3,4], this triggers senescence in normal cells and replicative capacity losing. The Senescent cells increased with inflammatory cytosine secreting, age and well-studied impacts in degenerative diseases and aging pathology[5]. However, the p-53 lacking in pre-malignant cells by passes senescence and continues dividing. The repair of DNA double strand break processed uncapped ands by machinery that leading to fusions and instability in chromosome, which lead to cells kills, but malignant transformation drives in the survivors[6]. Up regulate telomeres occurred in several survivors to telomeres maintain for continues proliferation, so approximately 15% use the pathway of alternative lengthening of telomeres (ALT)[7]. Demonstrate the critical effect of telomeres in aging and cancer, the telomeres shorten rate can profoundly impact in the stability of genome, like an organism well-being and health span.

Several factors contributed in the accelerated telomere shortening like genetic and environmental factors, the more cited underlying mechanism is oxidative stress (OS), which generated by unbalance between free radicals and antioxidant mechanisms, furthermore its involved in the etiology of different disease like cancer, pulmonary, neurological and cardiovascular diseases, diabetes atherosclerosis, arthritis and obesity[8-12]. Several of these diseases are the primary ROS source via mitochondrial dysfunction or/and inflammation, the ROS is produced by immune cells because of injury or infection and by oxygen metabolism, moreover it raised in chronic inflammation sites and is common in chronic inflammatory disorders like Barrett's esophagus, ulcerative colitis and hepatitis[13]. Epidemiology studies found that about 20% of cancers is caused by Chronic inflammation and it is main risk factor of aging-related diseases[13,14]. Environmental exposures factors are associated with elevated Oxidative stress as well as smoking, radon, pollution molecules, toxic metals, pesticides and ultraviolet light[15-17]. Likewise, numerous reports have been demonstrated that mitochondrial dysfunction and inflammation contributed in the ROS generation like many cancers and associated with telomere shortening acceleration[18,19]. The average of telomere length test in white blood cells is depended in These experiments[20,21]. Hear we discussed the role of OS in accelerating telomere length reduction in human, animal and cell line by evidences in different studies.

**Antioxidants Molecules:** The mitochondrion has significant role in the cell survival, because it contributed in the generation of ATP in the respiratory chain by electron transport enzyme complexes, in which ROS, like superoxide radical ($O_2^{\bullet -}$) are always production by electron transfer to molecular oxygen in complexes I (Nicotine adenine dinucleotide reduced, ubiquinone oxidoreductase) (NADH)-(ubiquinol-cytochrome c oxidoreductase) III of the inner membrane of mitochondria[22].

In the normal conditions, ROS represented as second messengers involved in some signaling pathways to some processes maintain such as growth, homeostasis and normal aerobic organisms development[23,24]. The Oxidative Stress (OS) happened in an imbalance between oxidants and antioxidant mechanisms, where the first presence in a higher proportion[24,25]. As reported, ROS like the $O_2^{\bullet -}$ are produced via the electron transport chain and its transformed to hydrogen peroxide ($H_2O_2$) in the existence of transition metals like $Fe^{3+}$, that becomes hydroxyl radical ($^{\bullet}OH$) with $O_2^{\bullet -}$ during Fenton and Haber-Weiss reactions[26], oxygen singlet ($^1O_2$) and Hydroxyl radical can produce DNA adducts, like 8-hydroxy-2-deoxyguanosine (8-OHdG)-TG, 8-OHdG results from the $^{\bullet}OH$ linked with the eighth carbon of the guanine[27], which transformed to its oxidized base 8-oxo-7-8-dihydro-2-deoxyguanosine (8-oxodG) via reaction of ketoenol tautomerism, it is considered the

most important oxidative damage, it forms approximately 100,000-8-oxodG in single cell every day[28,29].

Although of elevation in ROS in the body, antioxidant defense mechanisms were generated via exogenous and endogenous mechanisms to elimination ROS impacts directly or indirectly, moreover, studies found other oxidative molecules like reactive nitrogen species (RNS) or reactive sulfur species[30,31]. On the other hand, $O_2^{\bullet-}$ can transform by superoxide dismutase enzyme (SOD)-$H_2O_2$, that is converted to less toxic molecules by glutathione peroxides (GPx ) or catalase (CAT) enzymes[22]. Gradually oxidative damage raised over time because of decline in antioxidant mechanisms with age[32]. The OS theory has been proposed a direct cause for aging, according to the molecular disorder produced by the accumulation of free radical[33] and alteration of redox homeostasis lead to age-related diseases[34-37].

**Telomere Shortening / Dysfunction by Oxidative Stress:** In recent years, many studies have been observed the oxidative stress biomarkers were associated with telomere length reduction in WBC[39]. Same results were found in perceived and higher inflammatory loads and higher psychological stress populations[40]. In spite of subjects interesting, the information conclusion is difficult from these kinds of studies. More research about direct association of OS in homeostasis of telomere length derived from inflamed tissues report. High level of ROS and pre-neoplastic lesions development are characterizations of Chronic inflammatory diseases which can lead to cancer. Patients with Barrett's esophagus and Ulcerative colitis (UC) have shortened telomeres in affected mucosa than controls individuals[41]. Reports found shorter telomeres associated with infiltrating leukocytes and chromosomal instability[42,43], in addition to liver cirrhosis and inflamed livers from chronic hepatitis, atherosclerotic lesions which have also shorter telomere length in compared with unaffected tissues[44,45]. Telomere shortening is caused by Hyper-proliferation cells. However, in a review found that the rates of natural telomere shortening prostate cells need about most years of proliferation to reach the sensitive telomere lengths belong to the oxidative stress role in the precancerous prostatic intra epithelial neoplasia (PIN) and prostatic inflammatory atrophy and[46]. In sporadic disease the telomere shortening Mechanisms are under investigation, so, it may be related to OS[47].

In cell culture studies, Numerous reports found that OS-ROS exposure factors hasten telomere shortening, while free radical scavenger and antioxidant are eliminated shortening rates and elevated proliferative lifespan[48].

**Telomere Changes Induced via Oxidative Stress Mechanisms:** The telomere shorting mechanisms by oxidative stress have been elucidated by Several models, the OS induced cell death or senescence is one of these mechanisms, consequences to survivors undergo more cell proliferation that caused telomere shortening. its does not clarified hasten telomere shortening in non-cytologic and mild OS conditions[48]. More cited study proposed that ROS caused direct single strand cutting at telomeres, or as lesion repair intermediates causes replication fork dysfunction and telomere loss[48]. Otherwise, lesions can accumulate un replicated ssDNA in telomere and represented as fragile telomeres via multi-telemetric injury at chromatid ends[49]. In non-proliferative cells proliferation interference does not clarified how OS impacts telomeres. Some probabilities are that oxidative injury interplay with shelter in is association or transcription at telomeres into TERRA transcripts, oxidative injury mechanisms cause alteration in repeat number of telomere.

**Damage Telemetric DNA by ROS:** Different ROSs reacted with DNA causes more than 100 kinds of oxidative damaged bases, include pyrimidine and purines damages, like single strand breaks and a basic sites. Guanine is more common oxidation to generating 8-oxoG, that its more susceptible to oxidation, finally lead to hydantoin lesions[50,51]. Biochemical evidences observed that TTAGGG repeats are favorite location for iron interaction mediated Fenton reactions, to form hydroxyl radicals that remove 5 of GGG[52,53]. Likewise, some studies mentioned SSBs-8-oxoG in cellular telomeres exposure to oxidation condition in compared with other DNA sequence types[54,55]. Another study implemented by Aeby[56] mentioned that peroxiredoxin 1 (PRDX1), that work as $H_2O_2$ scavenger is found in high level in telomeres and its depleted leads to DNA damage at telomeres. In telomeres there was fluctuation about the increased of oxidative damage were happened based on the decreased repair or/and increased damage susceptibility. However in the structure of folded telemetric G-quadruplex complex, 8-oxoG molecules cannot be repaired[57]. Cellular researches proposed that shelter in protein TRF2 could interplay with BER[58,59].

**Oxidative Base Damage Correction by Base Excision Repair:** Base excision repair is contributed in several oxidative lesions repaired, for genome stability maintains and maintains telomeres. The accumulation of these lesions leads to carcinogenesis due to cytotoxic or mutagenic effects[60]. The mono-functional DNA glycosylase in BER detection specific DNA damage and removing it to form a basic site. A basic site generate by cleaves 5 via APE1 endonuclease to form an SSB with a 5 sugar phosphate and a 3 hydroxyl and. DNA polymerase (Pol) β excised 5 sugar phosphate by lyase function, in addition to template DNA synthesis, gap is filled, then ligated nicks by DNA ligase I-III[61]. Furthermore, these steps are conserved, some sub-pathways of BER assisted by further proteins. five glycosylase In mammalian cells recognized oxidative base injury like (OGG1-NEIL1-NEIL2-NEIL3 and NTHL1)[62,63]. They are bi-functional glycosylase, for excision the injury base and break the strand of DNA 3 to a basic site and then APE1 removed 3 blocking sugar or phosphate group or polynucleotide kinase[62,63]. In normal conditions BER used single nucleotide replacement, even so if refractory of 5 end to Pol β processing, Pol δ-ε put some bases, to form a offered DNA flap that is breaked via FEN1 endonuclease[64].

**The 8-oxoG Telomeres Processing:** The 8-oxoG is an important oxidative injury. In form of 8-oxoG, OGG1 glycosylase discriminate the complement C, to form a basic site by removing the lesion. Studies observe that OGG1 glycosylase function is enhance by XPC, NEIL1 and APE1[65,66]. OGG1 can more process this lesion with AP-lyase function, nevertheless strong affinity of OGG1 for a basic sites and may trap by its own product[65-67]. Furthermore, the deoxyribose moiety is removes by APE1 endonuclease to form SSB. Moreover, the 8-oxoG in single strand DNA cannot remove by OGG1[57].

This lead to ask about how the 8-oxoG is repaired if it located in telomere ssDNA regions Remarkably, in yeast study, the OGG1 deletion strain has short telomere than normal strain[68]. In vivo The longer telomere is observed in mice with Ogg1$^{-/-}$, but in vitro pro-oxidant conditions of cell culture demonstrated decreased in telomere length, malformation and loss in compared to control group[69]. This may occur a hormesis situation, little amount of 8-oxoG at telomeres enhanced lengthening, while large amount lead to telomere lack and degradation. Moreover, a 8-oxoG in ssDNA telomere causes folded G-quadruplex complex disruption which obstructs telomeres loading, thus enhancing telomere elongation[70]. On the other hand, the synergies of OS with unrepaired 8-oxoG to stimulate telomere loss in cell with Ogg1-/- is under investigation, because this lesion cannot prevent replication or transcription of DNA. The large amounts of 8-oxoG in telomeres cause shelterin destruction[71] or companied with other ROS-injuries like SSBs, oxidized pyrimidine to telomere dysfunction and processing.

Here again, when 8-oxoG escapes from repair mechanism, a round DNA replication can cause an opposite 8-oxoG misincorporation. Telemetric sequence alteration would lead to shelter in binding disruption. A opposite 8-oxoG was excised via MUTYH glycosylase forming a gap that would fill by Pol β-Pol λ in BER[72]. When the error is not repaired the motif sequences change TTA(8-oxoG)GG repeats to TTATGG that didn't observed commonly[73]. This referred to that either 8-oxoG is which MUTYH efficiently excise A opposite 8-oxoG at telomeres to eliminate mutations or well repaired at telomeres prior to replication, the OGG1 and MUTYH deficient cells need to be sequenced telomeres motifs which under oxidative stress conditions to discriminate the 8-oxoG mutagenic potential at telomeres. Biochemical studies have been found that free bases are more possible to oxidative injury than bases in DNA duplex and chromatin. Likewise, cells have machinery like MTH1, that hydrolyze damage dNTPs before insertion in genome during DNA replication[74]. Oxidized dNTPs perhaps more harmful to telomeres than oxidative base injury in the DNA duplex, during replication The 8-oxodGTP incorporation opposite A would change TTAGGG repeats to GTAGGG-TGAGGG. Notably these motifs are common in telomere sequencing reports[73]. On the other hand, during telomere extension telomeres can insert 8-oxodGTP, which leads to misincorporated the oxidized dGTP opposite A[56-70]. Lee *et al.*[73] mentioned that GTAGGG motif high percentage observed in distal telomere sites in cells with telomeres positive proposed that formed by telomeres errors, Consistent with 8-oxodGTP acute MTH1 deficient raised telomere missing and cell death in cancer cells with telomeres positive have short telomeres, but not in longer telomere tumor cell[56-70]. This proposed that 8-oxodGTP and oxidized form of dATP, that are excised by MTH1, blocked telomeres restoration of critically short telomeres. Several tumor cell lines are more sensitive to MTH1 blocking, in

contrast with normal cells that depended on telomeres function for short-term survival[75]. The role of MTH1 blocking in telomeres mutagenesis still under investigations. In spite of telomeres chain terminator of 8-oxodGTP, factors like POT1-TPP1, may help extension of telomeres following misincorporation of dNTPs damaged in cells[76].

**Other Oxidized Purines Types Processing:** Biochemical reported other oxidized nucleotide that are more toxic belong to its ability to prevent DNA replication, While 8-oxoG is primarily mutagenic, the other oxidized purines are cytotoxic effect according to their ability to DNA replication and transcription block. Belong to lower redox potential of 8-oxoG than the unmodified bases, further oxidized to other lesions can be occurred like guanidinohydantoin (Gh) and spiroiminodihydantoin (Sp)[77]. These destruction distorting hydantoin lesions implicated DNA transcription and replication[78,79], however, it can be removed by NEIL glycosylase enzymes[80]. Notably, mNeil3-NEIL1 excise Gh and Sp from structures of telemetric G-quadruplex and single strand DNA, while 8-oxoG don't be corrected[57]. The lesions processing in telemetric ssDNA and G-quadruplexes has significant contribution in telomere integrity. Reports have been shown that NEIL3 in telomeres through the S/G2 cell cycle-NEIL3 deficiency elevate telomere missing, aberrations and fusions and resultant anaphase DNA bridges[81]. The offending lesions contributed of telomere missing is difficult to discriminate as NEIL glycosylase excise some injury kinds such as oxidized pyrimidine and ring opened 2-6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG). Notably, mice with *Ogg1*$^{-/-}$-*Neil2*$^{-/-}$ showed high susceptibility to LPS and inflammation stimulated by OS[82,83]. Because of implicated of NEIL2 in BER through transcription, interfere may be happened between unrepaired hydantoin lesions with telemetric TERRA transcripts generation. The Roles of NEIL1 in telomeres still under investigation. However, triple knockout mice (*Neil1*-*Neil2*-Neil3) did not elucidate telomere shortening[84].

**Oxidized Pyrimidine Processing:** Free radicals can be oxidized Pyrimidine to generate different lesions as well as 5-hydroxy cytosine, Tg and 5-hydroxy uracil. The Tg is the more wide thymine oxidation injury with cytotoxic effects according to its ability to DNA replication block[85]. These lesions also can be removed by either NEIL glycosylase in duplex or ssDNA-NTHL1 glycosylase in duplex DNA[62,63]. Rather than, just Neil3 has strong preference to remove Tg from a telemetric G-quadruplex than non-telemetric duplex DNA[57]. Thereby , Tg lesions in unrepaired form may be partly contributed of defects in the telomere in cells with deficient Neil3 and/or Neil2[81-83]. *Nth1*$^{-/-}$ mice showed higher oxidized pyrimidine frequency. Several studies indicated that a single Tg present tiny distortion telemetric G-quadruplexes , The Tg causes changes in the structural conformations and the telemetric G-quadruplex dynamics in a way that prefer telomeres binding[73]. These reports prove implication of Tg in telomere defects via interplay with telomere replication and telomeres inhibition.

**Repair Systems in Oxidative Base Damage Processing:** In addition to BER proteins other repair systems also promote correct oxidative injury, such as, Nek7 kinase is enrolled to telomeres after exposure to superoxide anion, and shelter in TRF1 stabilizes[86]. Xeroderma Pigmentosum (XP) complementation group C protein, that is an integral composition of nucleotide excision repair (NER), stimulate OGG1 and thymine DNA glycosylase activity *in vitro*[87,88]. Furthermore, CSB (Cockayne Syndrome Type B)-XPG, a structure-specific endonuclease stimulate NTH1-NEIL2 glycosylase activity[89,90]. Cell lines with XPB-XPC-XPD and CSB deficient exposed to oxidants condition elucidated an oxidized purine repair disrupt, elevated cell mutagenesis and death compared with normal cells[87,90-92]. likewise, some NER proteins have protected telomeres against oxidative DNA injury. Mice with *Xpc*$^{-/-}$ grown at 20% $O_2$ causes a fragile telomere[93]. Deficient XPB-XPD of Human cells exposure to $H_2O_2$demonstrated high percentage of chromosome ends missing telemetric DNA[90]. Remarkably, some reports mentioned that XPA does not impact in telomere specific oxidative repair[87-90]. These proteins protect telomere against oxidative damage by stimulate BER or oxidative damage removing.

Moreover, in human cells Mismatch repair also involved in repair oxidative damage. losing of mismatch repair proteins MSH2-MLH1 increased the amount of 8-oxoG in cell lines under $H_2O_2$[94]. Its can be reduced with MTH1 over expression , referred to MMR adding 8-oxoG misincorporated through repair or replication. Notably, the MMR complex MutSα discriminate 8-oxoG opposite A-C very weak, but has robust affinity of 8-oxoG opposite T-G[95]. While these mispairings are unlikely, 8-oxoG opposite C its favorite via OGG1-A opposite 8-oxoG is favorite by MUTYH, thus, it indicated the mechanism

that evolved by cells to treat the other two 8-oxoG pairings, by MutSα. Reports are also referred to influence proteins of MMR possibility are essential to protect telomeres from oxidative injury.

**Defects in Oxidative Lesions Repair Systems:** Oxidative DNA injury processing can be further discriminated than initial injury, if toxic intermediates increased in the repair mechanism that are not fully understood. function of PARP1/2-poly(ADP-ribosyl)ation (PAR) in BER following nucleotide injury transform to an SSB. Otherwise, the impact of repair system in telomeres protect against OS still under investigation. Studies found extensive telomere shortening in cells with *PARP1*$^{-/-}$ mice[96,97]. The Blocking of PARP1 in HeLa cells, which exposed to 20% $O_2$, supported these results[98]. Notably, the activity of telomeres didn't change in cells with *PARP1*$^{-/-}$ or *PARP2*$^{-/-}$, ruling to telomeres activity modulation by PARP enzymes. Furthermore, these cells demonstrated a significant elevation in end-to-end fusions of chromosome via 26 population doubling. The poly(ADP-ribose) glycohydrolase (PARG) depletion, that is involved in PAR degradation, protects against telomere destruction stimulate by irradiation[99]. Studies found at damaged telomeres PARP1-PARP2 interplay with shelter in TRF2 that perhaps regulate PARP1/2[100,101]. These reports demonstrate that the telomere deficiency found in the lack of PARP1-PARP2 most likely increase from aborted BER of base injury.

Evidences proposed when ssDNA intermediates that create through BER persist or accumulate, they can cause collapse the replication fork and subsequent DSB formation[102]. SSBs repair Failures leads to some neurological disorders[103]. The SSBs or processing impact of oxidative injury in telomeres in normal cell still studied. The repair of clustered injuries on opposing strands can also causes Duple strand break (DSB)[104].

Its important to mention, the DSB accuracy and efficiency repair at the telomeres can be changed via shelter in proteins and the highly repetitive structure of the sequence[105].

## CONCLUSION

Studies proved that OS has significant role in the telomere shortening accelerated and dysfunction in human tissues, cell culture and in experiments. some mechanisms have been suggested to demonstrate how ROS high level effect on the telomere length homeostasis., belong to the high effective of ROS in cell components, further studies must be implemented to explain if the telomeres legend affected by direct or indirect ROS impacts.

## REFERENCES


1. Harley, C.B., A.B. Futcher and C.W. Greider, 1990. Telomeres shorten during ageing of human fibroblasts. Nature, 345: 458-460.
2. Palm, W. and T. de Lange, 2008. How shelterin protects mammalian telomeres. Annual Rev. Genet., 42: 301-334.
3. Fagagna, F.D., M.P. Hande, W.M. Tong, P.M. Lansdorp, Z.Q. Wang and S.P. Jackson, 1999. Functions of poly(ADP-ribose) polymerase in controlling telomere length and chromosomal stability. Nat. Genet., 23: 76-80.
4. de Lange, T., 2009. How telomeres solve the end-protection problem. Science, 326: 948-952.
5. Campisi, J., J.K. Andersen, P. Kapahi and S. Melov, 2011. Cellular senescence: A link between cancer and age-related degenerative disease? Seminars Cancer Biol., 21: 354-359.
6. Artandi, S.E., S. Chang, S.L. Lee, S. Alson, G.J. Gottlieb, L. Chin and R.A. DePinho, 2000. Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. Nature, 406: 641-645.
7. Opresko, P.L. and J.W. Shay, 2017. Telomere-associated aging disorders. Ageing Res. Rev., 33: 52-66.
8. Hegde, M.L., A.K. Mantha, T.K. Hazra, K.K. Bhakat, S. Mitra and B. Szczesny, 2012. Oxidative genome damage and its repair: Implications in aging and neurodegenerative diseases. Mech. Ageing Dev., 133: 157-168.
9. Lonkar, P. and P.C. Dedon, 2011. Reactive species and DNA damage in chronic inflammation: Reconciling chemical mechanisms and biological fates. Int. J. Cancer, 128: 1999-2009.
10. Malinin, N.L., X.Z. West and T.V. Byzova, 2011. Oxidation as "the stress of life". Aging, 3: 906-910.
11. Mao, X., C. Gu, D. Chen, B. Yu and J. He, 2017. Oxidative stress-induced diseases and tea polyphenols. Oncotarget, 8: 81649-81661.
12. Reuter, S., S.C. Gupta, M.M. Chaturvedi and B.B. Aggarwal, 2010. Oxidative stress, inflammation, and cancer: How are they linked?. Free Radical Biol. Med., 49: 1603-1616.
13. Bouvard, V., R. Baan, K. Straif, Y. Grosse and B. Secretan et al., 2009. A review of human

carcinogens-part b: Biological agents. Lancet Oncol., 10: 321-322.
14. Aseervatham, G.S.B., T. Sivasudha, R. Jeyadevi and D.A. Ananth, 2013. Environmental factors and unhealthy lifestyle influence oxidative stress in humans-an overview. Environ. Sci. Pollut. Res., 20: 4356-4369.
15. Baltazar, M.T., R.J. Dinis-Oliveira, M.D. Bastos, A.M. Tsatsakis, J.A. Duarte and F. Carvalho, 2014. Pesticides exposure as etiological factors of parkinson's disease and other neurodegenerative diseases-a mechanistic approach. Toxicol. Lett., 230: 85-103.
16. Poljšak, B. and R. Fink, 2014. The protective role of antioxidants in the defence against ros/rns-mediated environmental pollution. Oxidative Med. Cell. Long., 2014: 1-22.
17. Sanders, J.L., A. Iannaccone, R.M. Boudreau, Y.P. Conley and P.L. Opresko et al. 2011. The association of cataract with leukocyte telomere length in older adults: Defining a new marker of aging. J. Gerontol. Biol. Sci. Med. Sci., 66: 639-645.
18. Zhang, J., G. Rane, X. Dai, M.K. Shanmugam and F. Arfuso et al., 2016. Ageing and the telomere connection: An intimate relationship with inflammation. Ageing Res. Rev., 25: 55-69.
19. Martens, D.S. and T.S. Nawrot, 2016. Air pollution stress and the aging phenotype: The telomere connection. Curr. Environ. Health Rep., 3: 258-269.
20. Zhang, X., S. Lin, W.E. Funk and L. Hou, 2013. Environmental and occupational exposure to chemicals and telomere length in human studies. Occup. Environ. Med., 70: 743-749.
21. Koju, N., A. Taleb, J. Zhou, G. Lv and J. Yang et al., 2019. Pharmacological strategies to lower crosstalk between nicotinamide adenine dinucleotide phosphate (nadph) oxidase and mitochondria. Biomed. Pharmacother., 111: 1478-1498.
22. Burton, G.J. and E. Jauniaux, 2011. Oxidative stress. Best Pract. Res. Clin. Obstet. Gynaecol., 25: 287-299.
23. Rosado-Pérez, J., I. Aguiñiga-Sánchez, T.L. Arista-Ugalde, E. Santiago-Osorio and V.M. Mendoza-Núñez, 2019. The biological significance of oxidative stress, effects of fruits as natural edible antioxidants. Curr. Pharm. Des., 24: 4807-4824.
24. Betteridge, D.J., 2000. What is oxidative stress?. Metabolism, 49: 3-8.
25. Thomas, D.D., 2013. Oxidative stress. In: Encyclopedia of Biophysics, Roberts, G.C.K., (Ed.)., Springer Berlin Heidelberg, Berlin, Heidelberg, ISBN-28: 9783642167119, 9783642167126, pp: 1813-1818.
26. Kehrer, J.P., 2000. The haber–weiss reaction and mechanisms of toxicity. Toxicology, 149: 43-50.
27. Lindahl, T. and D.E. Barnes, 2000. Repair of endogenous DNA damage. Cold Spring Harbor Symposia Quantit. Biol., 65: 127-134.
28. Fouquerel, E., R.P. Barnes, S. Uttam, S.C. Watkins, M.P. Bruchez and P.L. Opresko, 2019. Targeted and persistent 8-oxoguanine base damage at telomeres promotes telomere loss and crisis. Mol. Cell, 75: 117-130.
29. Urbaniak, S.K., K. Boguszewska, M. Szewczuk, J. Kazmierczak-Baranska and B.T. Karwowski, 2020. 8-Oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) as a potential biomarker for gestational diabetes mellitus (GDM) development. Molecules, Vol. 25 .10.3390/molecules25010202.
30. Mut-Salud, N., P.J. Álvarez, J.M. Garrido, E. Carrasco, A. Aránega and F. Rodríguez-Serrano, 2016. Antioxidant intake and antitumor therapy: Toward nutritional recommendations for optimal results. Oxidative Med. Cell. Longev., Vol. 2016 .10.1155/2016/6719534.
31. Salehi, B., M. Martorell, J. Arbiser, A. Sureda and N. Martins et al., 2018. Antioxidants: Positive or negative actors?. Biomolecules, Vol. 8 .10.3390/biom8040124.
32. Osterod, M., 2001. Age-related and tissue-specific accumulation of oxidative DNA base damage in 7, 8-dihydro-8-oxoguanine-DNA glycosylase (Ogg1) deficient mice. Carcinogenesis, 22: 1459-1463.
33. Harman, D., 1992. Free radical theory of aging. Mutat. Res. Aging, 275: 257-266.
34. Saretzki, G. and T.V. Zglinicki, 2002. Replicative aging, telomeres, and oxidative stress. Ann. New York Acad. Sci., 959: 24-29.
35. Forman, H.J., 2016. Redox signaling: An evolution from free radicals to aging. Free Radical Biol. Med., 97: 398-407.
36. Liguori, I., G. Russo, F. Curcio, G. Bulli and L. Aran et al., 2018. Oxidative stress, aging, and diseases. Clin. Interv. Aging, 13: 757-772.
37. León, R.M.L., M.R. Cedeño, M.R.J. Rivero, P.D.L. García and G.L. Bordón, 2018. La teoría del estrés oxidativo como causa directa del envejecimiento celular. Medisur, 16: 699-710.
38. Reichert, S. and A. Stier, 2017. Does oxidative stress shorten telomeres In vivo ? A review. Biol. Lett., Vol. 13 .10.1098/rsbl.2017.0463.
39. O'Donovan, A., M.S. Pantell, E. Puterman, F.S. Dhabhar and E.H. Blackburn et al. 2011. Cumulative

inflammatory load is associated with short leukocyte telomere length in the health, aging and body composition study PLoS One, Vol. 6 .10.1371/journal.pone.0019687.
40. Letsolo, B.T., R.E. Jones, J. Rowson, J.W. Grimstead, W.N. Keith, G.J.S. Jenkins and D.M. Baird, 2017. Extensive telomere erosion is consistent with localised clonal expansions in barrett's metaplAsia. PLOS ONE, Vol. 12 .10.1371/journal.pone.0174833.
41. Baird, D.M., J. Rowson, D. Wynford-Thomas and D. Kipling, 2003. Extensive allelic variation and ultrashort telomeres in senescent human cells. Nat. Genet., 33: 203-207.
42. Risques, R.A., L.A. Lai, C. Himmetoglu, A. Ebaee and L. Li et al., 2011. Ulcerative colitis–associated colorectal cancer arises in a field of short telomeres, senescence and inflammation. Cancer Res., 71: 1669-1679.
43. Nzietchueng, R., M. Elfarra, J. Nloga, C. Labat and J.P. Carteaux et al., 2011. Telomere length in vascular tissues from patients with atherosclerotic disease. J. Nutr. Health Aging, 15: 153-156.
44. Rey, S., C. Quintavalle, K. Burmeister, D. Calabrese and M. Schlageter et al., 2017. Liver damage and senescence increases in patients developing hepatocellular carcinoma. J. Gastroenterol. Hepatol., 32: 1480-1486.
45. Graham, M.K. and A. Meeker, 2017. Telomeres and telomerase in prostate cancer development and therapy. Nat. Rev. Urol., 14: 607-619.
46. Kliment, C.R. and T.D. Oury, 2010. Oxidative stress, extracellular matrix targets, and idiopathic pulmonary fibrosis. Free Radical Biol. Med., 49: 707-717.
47. von Zglinicki, T., 2002. Oxidative stress shortens telomeres. Trends Biochem. Sci., 27: 339-344.
48. Sfeir, A., S.T. Kosiyatrakul, D. Hockemeyer, S.L. MacRae, J. Karlseder, C.L. Schildkraut and T. de Lange, 2009. Mammalian telomeres resemble fragile sites and require trf1 for efficient replication. Cell, 138: 90-103.
49. Cadet, J. and J.R. Wagner, 2013. Dna base damage by reactive oxygen species, oxidizing agents, and UV radiation. Cold Spring Harbor Perspect. Biol., 5: 12559-12559.
50. Fleming, A.M. and C.J. Burrows, 2017. Formation and processing of DNA damage substrates for the hneil enzymes. Free Radical Biol. Med., 107: 35-52.
51. Oikawa, S. and S. Kawanishi, 1999. Site-specific DNA damage at ggg sequence by oxidative stress may accelerate telomere shortening. FEBS Lett., 453: 365-368.
52. Oikawa, S., S. Tada-Oikawa and S. Kawanishi, 2001. Site-specific DNA damage at the ggg sequence by uva involves acceleration of telomere shortening. Biochemistry, 40: 4763-4768.
53. Coluzzi, E., M. Colamartino, R. Cozzi, S. Leone, C. Meneghini, N. O'Callaghan and A. Sgura, 2014. Oxidative stress induces persistent telomeric DNA damage responsible for nuclear morphology change in mammalian cells. PLoS ONE, Vol. 9.
54. Rhee, D.B., A. Ghosh, J. Lu, V.A. Bohr and Y. Liu, 2011. Factors that influence telomeric oxidative base damage and repair by DNA glycosylase ogg1. DNA Repair, 10: 34-44.
55. Aeby, E., W. Ahmed, S. Redon, V. Simanis and J. Lingner, 2016. Peroxiredoxin 1 protects telomeres from oxidative damage and preserves telomeric DNA for extension by telomerase. Cell Rep., 17: 3107-3114.
56. Zhou, J., M. Liu, A.M. Fleming, C.J. Burrows and S.S. Wallace, 2013. Neil3 and neil1 DNA glycosylases remove oxidative damages from quadruplex DNA and exhibit preferences for lesions in the telomeric sequence context. J. Bio. Chem., 288: 27263-27272.
57. Richter, T., G. Saretzki, G. Nelson, M. Melcher, S. Olijslagers and T. von Zglinicki, 2007. Trf2 overexpression diminishes repair of telomeric single-strand breaks and accelerates telomere shortening in human fibroblasts. Mech. Ageing Dev., 128: 340-345.
58. Miller, A.S., L. Balakrishnan, N.A. Buncher, P.L. Opresko and R.A. Bambara, 2012. Telomere proteins POT1, TRF1 and TRF2 augment long-patch base excision repair in vitro. Cell Cycle, 11: 998-1007.
59. Wallace, S.S., D.L. Murphy and J.B. Sweasy, 2012. Base excision repair and cancer. Cancer Lett., 327: 73-89.
60. Srivastava, D.K., B.J.V. Berg, R. Prasad, J.T. Molina, W.A. Beard, A.E. Tomkinson and S.H. Wilson, 1998. Mammalian abasic site base excision repair. J. Bio. Chem., 273: 21203-21209.
61. Krokan, H.E. and M. Bjoras, 2013. Base excision repair. Cold Spring Harbor Perspect. Biol., Vol. 5 .10.1101/cshperspect.a012583.
62. Wallace, S.S., 2013. Dna glycosylases search for and remove oxidized DNA bases. Environ. Mol. Mutagen., 54: 691-704.
63. Sobol, R.W., R. Prasad, A. Evenski, A. Baker, X.P. Yang, J.K. Horton and S.H. Wilson, 2000. The lyase activity of the DNA repair protein ß-polymerase protects from DNA-damage-induced cytotoxicity. Nature, 405: 807-810.
64. Hill, J.W., 2001. Stimulation of human 8-oxoguanine-DNA glycosylase by ap-endonuclease:

Potential coordination of the initial steps in base excision repair. Nucleic Acids Res., 29: 430-438.
65. Mokkapati, S.K., L. Wiederhold, T.K. Hazra and S. Mitra, 2004. Stimulation of DNA glycosylase activity of OGG1 by neil1: Fnctional collaboration between two human DNA glycosylases. Biochemistry, 43: 11596-11604.
66. Morland, I., L. Luna, E. Gustad, E. Seeberg and M. Bjørås, 2005. Product inhibition and magnesium modulate the dual reaction mode of hOgg1. DNA Repair, 4: 381-387.
67. Askree, S.H., T. Yehuda, S. Smolikov, R. Gurevich and J. Hawk et al., 2004. A genome-wide screen for Saccharomyces cerevisiae deletion mutants that affect telomere length. Proc. Nat. Acad. Sci., 101: 8658-8663.
68. Wang, Z., D.B. Rhee, J. Lu, C.T. Bohr and F. Zhou et al., 2010. Characterization of oxidative guanine damage and repair in mammalian telomeres. PLoS Genet., Vol. 6 .10.1371/journal.pgen.1000951.
69. Fouquerel, E., J. Lormand, A. Bose, H.T. Lee and G.S. Kim et al., 2016. Oxidative guanine base damage regulates human telomerase activity. Nat. Struct. Mol. Biol., 23: 1092-1100.
70. Lu, J. and Y. Liu, 2009. Deletion of ogg1 DNA glycosylase results in telomere base damage and length alteration in yeast. EMBO J., 29: 398-409.
71. Markkanen, E., 2017. Not breathing is not an option: How to deal with oxidative DNA damage. DNA Repair, 59: 82-105.
72. Lee, M., M. Hills, D. Conomos, M.D. Stutz and R.A. Dagg et al., 2013. Telomere extension by telomerase and alt generates variant repeats by mechanistically distinct processes. Nucleic Acids Res., 42: 1733-1746.
73. Rudd, S.G., N.C.K. Valerie and T. Helleday, 2016. Pathways controlling dNTP pools to maintain genome stability. DNA Repair, 44: 193-204.
74. Gad, H., T. Koolmeister, A.S. Jemth, S. Eshtad and S.A. Jacques et al., 2014. Mth1 inhibition eradicates cancer by preventing sanitation of the dntp pool. Nature, 508: 215-221.
75. Sale, J.E., A.R. Lehmann and R. Woodgate, 2012. Y-family DNA polymerases and their role in tolerance of cellular DNA damage. Nat. Rev. Mol. Cell Biol., 13: 141-152.
76. Luo, W., J.G. Muller, E.M. Rachlin and C.J. Burrows, 2001. Characterization of hydantoin products from one-electron oxidation of 8-Oxo-7, 8-dihydroguanosine in a nucleoside model. Chem. Res. Toxicol., 14: 927-938.
77. Henderson, P.T., J.C. Delaney, J.G. Muller, W.L. Neeley, S.R. Tannenbaum, C.J. Burrows and J.M. Essigmann, 2003. The hydantoin lesions formed from oxidation of 7, 8-dihydro-8-oxoguanine are potent sources of replication errors in vivo. Biochemistry, 42: 9257-9262.
78. Kolbanovskiy, M., M.A. Chowdhury, A. Nadkarni, S. Broyde, N.E. Geacintov, D.A. Scicchitano and V. Shafirovich, 2017. The nonbulky DNA lesions spiroiminodihydantoin and 5-guanidinohydantoin significantly block human RNA polymerase ii elongation In vitro. Biochemistry, 56: 3008-3018.
79. Zhou, J., J. Chan, M. Lambelé, T. Yusufzai and J. Stumpff et al., 2017. Neil3 repairs telomere damage during s phase to secure chromosome segregation at mitosis. Cell Rep., 20: 2044-2056.
80. Aguilera-Aguirre, L., A. Bacsi, Z. Radak, T.K. Hazra and S. Mitra *et al.*, 2014. Innate inflammation induced by the 8-oxoguanine DNA glycosylase-1-KRAS-NF-?B pathway. J. Immunol., 193: 4643-4653.
81. Chakraborty, A., M. Wakamiya, T. Venkova-Canova, R.K. Pandita and L. Aguilera-Aguirre *et al.*, 2015. Neil2-null mice accumulate oxidized DNA bases in the transcriptionally active sequences of the genome and are susceptible to innate inflammation. J. Bio. Chem., 290: 24636-24648.
82. Rolseth, V., L. Luna, A.K. Olsen, R. Suganthan and K. Scheffler *et al.*, 2017. No cancer predisposition or increased spontaneous mutation frequencies in neil DNA glycosylases-deficient mice. Sci. Rep., Vol. 7 .10.1038/s41598-017-04472-4.
83. McNulty, J.M., B. Jerkovic, P.H. Bolton and A.K. Basu, 1998. Replication inhibition and miscoding properties of DNA templates containing a site-specific Cis-thymine glycol or urea residue. Chem. Res. Toxicol., 11: 666-673.
84. Tan, R., S. Nakajima, Q. Wang, H. Sun and J. Xue et al., 2017. Nek7 protects telomeres from oxidative DNA damage by phosphorylation and stabilization of trf1. Mol. Cell, 65: 818-83100000.
85. D'Errico, M., E. Parlanti, M. Teson, B.M.B. de Jesus and P. Degan *et al.,* 2006. New functions of xpc in the protection of human skin cells from oxidative damage. EMBO J., 25: 4305-4315.
86. Shimizu, Y., 2003. Xeroderma pigmentosum group c protein interacts physically and functionally with thymine DNA glycosylase. EMBO J., 22: 164-173.
87. Aamann, M.D., C. Hvitby, V. Popuri, M. Muftuoglu and L. Lemminger *et al.,* 2014. Cockayne syndrome group b protein stimulates neil2 DNA glycosylase activity. Mech. Ageing Dev., 135: 1-14.
88. Klungland, A., M. Höss, D. Gunz, A. Constantinou and S.G. Clarkson *et al.,* 1999. Base excision repair of oxidative DNA damage activated by xpg protein. Mol. Cell, 3: 33-42.

89. Gopalakrishnan, K., G.K.M. Low, A.P.L. Ting, P. Srikanth, P. Slijepcevic and M.P. Hande, 2010. Hydrogen peroxide induced genomic instability in nucleotide excision repair-deficient lymphoblastoid cells. Genome Integrity, Vol. 1 .10.1186/2041-9414-1-16.
90. Melis, J.P.M., R.V. Kuiper, E. Zwart, J. Robinson and J.L.A. Pennings et al., 2013. Slow accumulation of mutations in Xpc-/- mice upon induction of oxidative stress. DNA Repair, Vol. 12 .10.1016/j.dnarep.2013.08.019.
91. Stout, G.J. and M.A. Blasco, 2013. Telomere length and telomerase activity impact the uv sensitivity syndrome xeroderma pigmentosum c. Cancer Res., 73: 1844-1854.
92. Colussi, C., E. Parlanti, P. Degan, G. Aquilina and D. Barnes et al., 2002. The mammalian mismatch repair pathway removes DNA 8-oxodgmp incorporated from the oxidized dntp pool. Curr. Biol., 12: 912-918.
93. Larson, E.D., K. Iams and J.T. Drummond, 2003. Strand-specific processing of 8-oxoguanine by the human mismatch repair pathway: Inefficient removal of 8-oxoguanine paired with adenine or cytosine. DNA Repair, 2: 1199-1210.
94. Fagagna, F.D., P.M. Reaper, L. Clay-Farrace, H. Fiegler and P. Carr *et al.*, 2003. A DNA damage checkpoint response in telomere-initiated senescence. Nature, 426: 194-198.
95. Stirzaker, C., P.C. Taberlay, A.L. Statham and S.J. Clark, 2014. Mining cancer methylomes: Prospects and challenges. Trends Genet., 30: 75-84.
96. Beneke, S., O. Cohausz, M. Malanga, P. Boukamp, F. Althaus and A. Bürkle, 2008. Rapid regulation of telomere length is mediated by poly(ADP-ribose) polymerase-1. Nucleic Acids Res., 36: 6309-6317.
97. Ame´, J.C., E. Fouquerel, L.R. Gauthier, D. Biard and F.D. Boussin et al., 2009. Radiation-induced mitotic catastrophe in parg-deficient cells. J. Cell Sci., 122: 1990-2002.
98. Dantzer, F., M.J. Giraud-Panis, I. Jaco, J.C. Amé and I. Schultz *et al.,* 2004. Functional interaction between poly(ADP-ribose) polymerase 2 (PARP-2) and trf2: Parp activity negatively regulates trf2. Mol. Cell. Biol., 24: 1595-1607.
99. Gomez, M., J. Wu, V. Schreiber, J. Dunlap, F. Dantzer, Y. Wang and Y. Liu, 2006. Parp1 is a trf2-associated poly(ADP-ribose)polymerase and protects eroded telomeres. Mol. Biol. Cell, 17: 1686-1696.
100. Zampieri, M., F. Ciccarone, R. Calabrese, C. Franceschi, A. Bürkle and P. Caiafa, 2015. Reconfiguration of DNA methylation in aging. Mech. Ageing Dev., 151: 60-70.
101. Rulten, S.L. and K.W. Caldecott, 2013. Dna strand break repair and neurodegeneration. DNA Repair, 12: 558-567.
102. Cannan, W.J., B.P. Tsang, S.S. Wallace and D.S. Pederson, 2014. Nucleosomes suppress the formation of double-strand DNA breaks during attempted base excision repair of clustered oxidative damages. J. Bio. Chem., 289: 19881-19893.
103. Doksani, Y. and T. de Lange, 2014. The role of double-strand break repair pathways at functional and dysfunctional telomeres. Cold Spring Harbor Perspect. Biol., Vol. 6.