HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Pharmacol Ther. 2021 April ; 220: 107742. doi:10.1016/j.pharmthera.2020.107742.

Telomeres in toxicology: Occupational health

Mohammad Shoeb[a,*], **Helen C.S. Meier**[b], **James M. Antonini**[a]

[a]Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV, United States of America

[b]Joseph J. Zilber School of Public Health, University of Wisconsin, Milwaukee, WI, United States of America

Abstract

The ends of chromosomes shorten at each round of cell division, and this process is thought to be affected by occupational exposures. Occupational hazards may alter telomere length homeostasis resulting in DNA damage, chromosome aberration, mutations, epigenetic alterations and inflammation. Therefore, for the protection of genetic material, nature has provided a unique nucleoprotein structure known as a telomere. Telomeres provide protection by averting an inappropriate activation of the DNA damage response (DDR) at chromosomal ends and preventing recognition of single and double strand DNA (ssDNA and dsDNA) breaks or chromosomal end-to-end fusion. Telomeres and their interacting six shelterin complex proteins in coordination act as inhibitors of DNA damage machinery by blocking DDR activation at chromosomes, thereby preventing the occurrence of genome instability, perturbed cell cycle, cellular senescence and apoptosis. However, inappropriate DNA repair may result in the inadequate distribution of genetic material during cell division, resulting in the eventual development of tumorigenesis and other pathologies. This article reviews the current literature on the association of changes in telomere length and its interacting proteins with different occupational exposures and the potential application of telomere length or changes in the regulatory proteins as potential biomarkers for exposure and health response, including recent findings and future perspectives.

Keywords

Telomere; Telomerase; Shelterin complex; Occupational exposures; DNA damage response; DNA damage

[*]Corresponding author at.: Centers for Disease Control and Prevention, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, 1000 Frederick Lane, Morgantown, WV 26505, United States of America. ywo7@cdc.gov (M. Shoeb).

Declaration of Competing Interest

The authors declare that they have no competing interests.

1. Introduction

As humans, we hope to enjoy a long and healthy life, but longevity tends to be dictated by our genes inherited from our parents. To protect our genome, nature evolved a cap-like structure at the end of chromosomes known as telomeres, that are composed of tandem repeats of hexanucleotides 5′-TTAGGG-3′ DNA sequences shielded with a group of six proteins called shelterin (Fig. 1). This complex facilitates the formation of hairpin like structure (T-loop and the D-loop) to safeguard chromosomal ends from degradation and activating the DNA damage response (DDR) (de Lange, 2005a; Greider, 1991; Griffith, Comeau, Rosenfield, et al., 1999). The term telomere was introduced by Muller and is derived from two Greek words, telos (terminus) and meros (part) (Muller, 1938). Telomeres avoid deleterious chromosomal fusions by covering the natural ends of linear chromosomes and distinguishing them from resembling DNA breaks. Apart from protecting our genome from degradation and chromosomal end-to-end fusion, telomeres also play a critical role in DNA repair mechanisms of dsDNA breaks with nonhomologous end-joining (NHEJ) to stabilize a broken genome, maintain the replicative potential of the cells, and serve as substrates for telomerase enzymes (Blackburn, 1990; de Lange, 2005b; Grach, 2013; Greider, 1996; Haber, 1999; Muller, 1938; Oeseburg, de Boer, van Gilst, & van der Harst, 2010). In the 1960s, Hayflick and Moorhead, using normal human fibroblasts, confirmed that the cells can divide up to 40 to 60 cycles with shortening of telomeres. This phenomenon of telomere shortening was named the ‘Hayflick Limit’ (Hayflick, 1965; Hayflick & Moorhead, 1961). Telomere length shortens with age with each round of cell division (Fig. 2A), consequently resulting in an end-replication problem (Watson, 1972; Greider & Blackburn, 1989 and Olovnikov, 1973. This problem occurs because of the incapability of the DNA polymerase enzyme to completely replicate the 5′ ends of the lagging strand due to unavailability of 3′-OH group to which a nucleotide can be added. The end-replication problem is avoided by the enzyme telomerase replicating the leading strand (5′–3′) before the RNA primer, with an -OH group, synthesizes the lagging strand (3′–5′) by the conventional DNA replication mechanism. To some extent, end replication is also untangled by the shelterin complex proteins with the recruiting of the enzyme telomerase (Giraud-Panis, Teixeira, Geli, & Gilson, 2010; Palm & de Lange, 2008; Price, Boltz, Chaiken, et al., 2010; Stewart, Wang, Chaiken, et al., 2012 and Wu, Liu, Ni, et al., 2012).

Elizabeth Blackburn and colleagues were awarded a Nobel prize for the discovery of “how chromosomes are protected by telomeres and the enzyme telomerase” in 2009. When telomeres become critically short, they activate DDR machinery or enter senescence (Fig. 2B) by arrest in the G1 phase of the cell cycle to prevent impending DNA damage. Cellular senescence is a complex process and could be beneficial (van Deursen, 2014) or deleterious (Baker, Childs, Durik, et al., 2016; Baker, Wijshake, Tchkonia, et al., 2011), depending on the circumstances and tissue-specific conditions. Senescent cells have been implicated in the development of pulmonary fibrosis (Schafer, White, Iijima, et al., 2017), atherosclerosis (Childs, Baker, Wijshake, et al., 2016), liver steatosis (Ogrodnik, Miwa, Tchkonia, et al., 2017) and other age-related diseases (Adnot, Amsellem, Boyer, et al., 2015). The measurement of telomere length homeostasis and the expression of proteins that regulate telomeres have been proposed as potential biomarkers to assess various occupational

exposures and possibly predict future development of disease pathologies. Here, we discuss how occupational exposures may impact telomere homeostasis and cause dysfunctional shelterin proteins contributing to DNA damage signaling and how altered telomeres and their associated regulatory proteins can be the source of genome instability leading to the induction and/or progression of occupational diseases and prognosis.

2. Telomere function, regulation and dysregulation

Telomeres are a duplex of G-rich tandem DNA sequences of TTAGGG repeats that prevent the recognition of chromosomal ends as dsDNA breaks, and thus conserve genomic stability. Single stranded G-rich telomeric DNA overhang ends consist of approximately 50 to 400 nucleotides beyond the complementary C-rich strand protruding toward the double-stranded region of the telomere (Doksani & de Lange, 2014). Telomeres are needed at the end of chromosomes to solve the end-replication problem, but they shorten during each cell division leading to cell cycle arrest, cellular senescence, and apoptosis. However, some telomere or possible associated regulatory proteins mutations, could by-pass cells from undergoing excessive telomere attrition thereby preventing cells from becoming senescent, leading to cell immortality and potentially increasing the prognosis of cellular immortalization and cancer (Meyerson, Counter, Eaton, et al., 1997; Shammas, 2011). Telomere length is maintained by an enzyme called telomerase (Blackburn, Greider, Henderson, et al., 1989; Greider & Blackburn, 1985). The telomerase is a reverse transcriptase ribonucleoprotein complex composed of telomerase reverse transcriptase (TERT), coupled with telomerase RNA component (TERC) (Gilson and Geli, 2007; Londono-Vallejo & Wellinger, 2012) that synthesize de novo the addition of TTAGGG repeats at the end of telomeres, thereby controlling excessive telomere shortening in multiplying cells (Greider & Blackburn, 1985, 1989).

Thus, the question becomes, how does the enzyme telomerase prevent excessive telomere shorting? DNA is double stranded, and its replication occurs from 5′ to 3′, which always has an -OH group available at the end to add another nucleotide, therefore allowing for the leading strand to replicate. However, the problem is with the lagging strand where the daughter strand cannot be elongated from 3′ to 5′ because of the absence of the -OH group. Hence, no nucleotide can be added at the end of the lagging strand, resulting in an end replication problem. Telomerase is a reverse transcriptase that binds to the 3′ overhang of the parent DNA, generating -OH groups that are available to the daughter DNA of the lagging strand and maintain telomere length.

Telomerase activity depends on the expression of TERT and TERC as well as on the cell type. For example, telomerase activity is nearly completely absent in somatic cells, whereas it is sufficiently expressed in embryonic stem cells (Blasco, 2005). Due to mutations in TERT (Horn, Figl, Rachakonda, et al., 2013; Liu, Zhang, Zhu, & Xing, 2018; Günes, Wezel, Southgate, & Bolenz, 2018;), more than 90% of cancers have significant levels of telomerase activity (Jafri, Ansari, Alqahtani, & Shay, 2016; Kim, Piatyszek, Prowse, et al., 1994; Shay & Bacchetti, 1997), whereas the other 10% maintain telomere length utilizing telomerase-independent mechanisms involved in the conservation of telomere length, known as alternative lengthening of telomeres (ALT) (Barthel, Wei, Tang, et al., 2017; Bryan,

Englezou, Dalla-Pozza, Dunham, & Reddel, 1997; Cesare and Reddel, 2010; Reddel, 2003; Lundblad & Blackburn, 1993). Maintenance of telomere length by a telomerease-independent mechanism, such as ALT, involves activation during genetic modification. Epigenetic irregularities [e.g., tumor protein 53 (p53)] promote approximately 15% of human cancer cells proliferation because of its genetically unstable nature)(Cesare, Kaul, Cohen, et al., 2009; Chen, Shen, Hsia, et al., 2017; Conomos, Pickett, & Reddel, 2013; Henson, Neumann, Yeager, & Reddel, 2002; Lovejoy, Li, Reisenweber, et al., 2012; Min, Wright, & Shay, 2017; Neumann, Watson, Noble, et al., 2013; Roake & Artandi, 2016). Activation of ALT pathways can also occur by utilizing a homologous recombination (HR) mechanism and its associated proteins, such as the MRN complex proteins (MRE11, RAD50, NSB1), NBN, and other proteins involved in structural maintenance of telomeres, including SMC5, SMC6, FANDCD2, FANCA, and FEN1 (Cesare et al., 2010; and Gocha, Harris, & Groden, 2013). Furthermore, long non-coding RNA termed as telomeric repeat-containing RNA (TERRA) are also involved in transcribing telomeric sequence by recruiting telomerase (Cusanelli, Romero, & Chartrand, 2013) at the telomere, specifically at the sub-telomeric region of 3′ end of chromosome (Azzalin, Reichenbach, Khoriauli, Giulotto, & Lingner, 2007). TERRA is an imperative regulatory factor in governing telomere length through its interaction with various protein complexes, such as shelterin (TRF2) and trimeric CST complex (CTC1, STN1, and TEN1) (Cusanelli et al., 2013).

To maintain telomere integrity, both telomeric strands (−ss and -ds) are shielded by a shelterin complex, composed of six different proteins; telomere repeat factors 1 and 2 (TRF1 and TRF2), Trf1-interacting protein 2 (TIN2), tripeptidyl peptidase 1 (TPP1), protection of telomere 1 (POT1), and repressor/activator protein 1 (RAP1)(Fig. 1). Two shelterin proteins, TRF1, and TRF2, directly bind to ds-telomeric-DNA, whereas POT1 binds to ss-telomeric-DNA and are held together by three other shelterin proteins, TIN2, TPP1, and RAP1, preventing them from being recognized as sites of DNA damage. The shelterin subunit TIN2 bridges the ds- and ss-telomeric-DNA. Furthermore, two components of the shelterin complex, TPP1 and POT1, are an integral part of telomerase activation through their association with TERT (Sandin & Rhodes, 2014). The shelterin complex protects and maintains telomeres by suppressing DNA repair machinery and formation of a T-loop structure at the telomeres. Apart from maintaining and regulating telomere structure, shelterin complex also prevent unwanted DNA repair. (de Lange, 2005a; de Lange, 2018).

The inhibition, removal, or dysfunction of the shelterin complex can result in alteration of telomeres and DNA damage inducing two powerful transducing kinases, ataxia telangiectasia and Rad3-related (ATR) and ataxia telangiectasia-mutated (ATM) (Fig. 3) that could become inappropriately active at the telomeres resulting in hyper-resection of the 5′ strand (Sfeir & de Lange, 2012). The double stranded shelterin component TRF2, suppresses ATM signaling pathways and becomes activated during dsDNA breaks by associating with the trimeric complex, MRN. The ATM kinase then phosphorylates the proteins in the chromatin, resulting in the accumulation of DNA damage foci such as 53BP1, MRN, γH2AX, and MDC1, and consequently marking that spot as a location of DNA damage (Attwooll, Akpinar, & Petrini, 2009; Celli & de Lange, 2005; Deng, Guo, Ferguson, & Chang, 2009; Dimitrova & de Lange, 2009; Stracker & Petrini, 2011). Shelterin component, POT1 suppresses ATR signaling and becomes activated when ssDNA is at a break in the

telomeric DNA by associating replication protein A (RPA) to ssDNA, thus explaining the elevated RPA level in S and G2 than in G1 at telomeres, as well as, the ATR kinase that phosphorylates proteins in the chromatin and subsequently accumulates in DNA damage foci which is then marked as a DNA damage site (de Lange, 2010). Other than phosphorylating proteins in the chromatin and activating DNA damage foci, the stimulation of ATM and ATR kinase can also enforce cell cycle arrest (through phosphorylation and activation of cell cycle components, CHK1/CHK2), activate p53 and inactivate CDC25 phosphatase (Fig. 4), thereby inhibiting the cell to transition from G1 to S phase where DNA replication occurs (Churikov & Price, 2008; Denchi & de Lange, 2007; Gong & de Lange, 2010).

3. Telomeres in toxicology: Association with occupational exposures

The information on the toxic effects of occupational exposures involving telomeres is limited. Exposure to various occupational hazards have been shown to cause alterations or mutation in chromosomes, triggering various disease conditions (Reste, Zvigule, & Zvagule, 2014). However, the understanding of these exposures on telomere stability is lacking and inconsistent because of aberrant telomere length after these exposures. For instance, both occupational and environmental exposures could lead to binary telomere length (short or long telomeres) resulting in inflammation, DNA damage, chromosome abnormality, and epigenetic modifications that may contribute to development of diseases, such as diabetes, fibrosis, neurodegeneration, abnormal cardiovascular events, and cancer (Armanios, 2012; Fitzpatrick, Kronmal, Gardner, et al., 2007; Hou, Zhang, Gawron, et al., 2012; Hou, Zhang, Wang, et al., 2012; Sampson, Winterbone, Hughes, Dozio, & Hughes, 2006; Shoeb, Mustafa, et al., 2020; Srinivas, Rachakonda, & Hielscher, 2019; Uziel, Singer, & Danicek, 2007; Weisburger & Williams, 1983). Molecular mechanisms of aberrant telomere length homeostasis due to occupational exposures are not fully understood. Due to the G-rich terminal region, telomere 3′ overhang has been observed to be more susceptible to oxidative modifications of guanine residues (Fouquerel, Lormand, Bose, et al., 2016; Houben, Moonen, van Schooten, & Hageman, 2008; Kawanishi & Oikawa, 2004). Because most chronic diseases are non-genetic and may occur due to various exposures, assessing an individual’s exposure history might be helpful in evaluating the origin of specific diseases (Rappaport, 2011; Rappaport & Smith, 2010). However, this has been proven difficult because of unknown and complicated exposure histories. Exposure assessment is important for occupational epidemiological studies that measure telomere. This can allow correlating exposure doses to alteration in telomere length homeostasis and provide meaningful interpretation of occupational risk. Importantly, mechanisms of telomere length alteration in workers exposed to various occupational hazards has not been well documented. Both extremely long and critically short telomeres have been associated with increased risk of cancer and other diseases. However, the mechanisms through which binary telomere length may contribute to development of various diseases remain unclear. Therefore, identification and quantification of telomere, its regulatory, and other telomere interacting proteins before, during, and after occupational exposures should be imperatively considered and needs to be systematically understood. Furthermore, analysis of telomere length homeostasis in isolated

cells and tissues may allow for the development and discovery of potential biomarkers of response in the assessment of toxicity associated with occupational agents.

4. Occupational exposure and telomere length

Conceptually, mitotic cells stop dividing due to critical shortening of telomere that will lead to cellular senescence and cell cycle arrest. However, as shown in Fig. 2B, some hazardous exposures may result in telomere shortening of the cells and then start expressing elevated telomerase activity that may be due to a mutation in TERT, possibly resulting in tumor formation (Barthel et al., 2017). On the other hand, increased telomere length may be due to increased telomerase expression that may result in elevated cancer development by increasing replicative capacity of those cells. Because senescent cells cannot undergo further replication, it is unlikely they will be involved in cancer development, tumor formation, and imminent DNA damage. However, at times senescent cells can express a senescence-associated secretory phenotype (SASP) that may result in tumor progression (Cahu, Bustany, & Sola, 2012). The telomere and its regulatory proteins are essential in promoting or inhibiting cancer. One of the mechanisms of cancer inhibition could be through induction of p53 and cellular senescence due to dysfunctional telomeres. Moreover, dysfunctional telomeres may promote initiation and progression of tumorigenesis through mutation or deletion of p53 and activation of TERT expression (Ding, Wu, Jaskelioff, et al., 2012; Hu, Sarah Hwang, Liesa, et al., 2012). This review will focus primarily on addressing alterations in telomere length after exposures in different occupational groups, primarily workers in the welding and silica industries. These specific industries were chosen as the International Agency for Research on Cancer (IARC) has classified welding fume (Guha, Loomis, et al., 2017) and crystalline silica/quartz (Guha, Straif, & Benbrahim-Tallaa, 2011) as Group 1 carcinogens in humans. In addition, the effect of exposure of other occupational hazards on telomere length are also discussed, including exposure of workers in the rubber and coal industries. IARC also has classified quartz, a constituent of coal (IARC – International Agency for Research on Cancer, 1997; International Agency for Research on Cancer (IARC), 2012a), and specific chemicals generated in the rubber industry as Group 1 carcinogens (International Agency for Research on Cancer (IARC), 2012b).

4.1. Welding industry

In the United States, approximately 581,000 classified welders are employed as full-time worker (https://datausa.io/profile/soc/514120/). Millions of other non-classified welders are exposed to welding fumes daily worldwide. Based on adequate epidemiology and limited animal studies, welding fume has been recently classified as a known carcinogen (Group 1) to humans by IARC (Guha et al., 2017). Welding fumes are a complex mixture of different cytotoxic, neurotoxic, and genotoxic metals (e.g., Cr, Ni, Mn, and Fe). Their metal composition is different depending on the types of electrodes/consumables used during the welding process, such as stainless steel or mild steel. Stainless steel welding fumes are primarily composed of Cr, Fe, Mn, and Ni, whereas mild steel fumes are composed of mostly Fe and Mn. The health effect of the greatest concern associated with welding fume exposure is lung cancer (Antonini, 2014; Martin, Guidotti, & Langard, 1997). Non-pulmonary health effects associated with welding fume exposure include cardiovascular

(Ibfelt, Bonde, & Hansen, 2010; Sjogren, Fossum, Lindh, & Weiner, 2002) and neurological disorders (Racette, 2014; Racette, McGee-Minnich, Moerlein, et al., 2001; Sriram, Lin, Jefferson, et al., 2010). An important characteristic of cancer is to alter or detour a normally dividing cell to a cancerous cell through disruption of telomere length homeostasis. Identification of biomarkers may impact the health of large number of welders by detecting early potential toxicological changes that are predictive of chronic diseases, specifically lung cancer (Ambroise, Wild, & Moulin, 2006; Hansen, Lauritsen, & Skytthe, 1996; Kendzia, Behrens, Jockel, et al., 2013; Vallieres, Pintos, Lavoue, et al., 2012).

Limited studies have established an association between welding fume exposure and telomere length in humans. Wong, De Vivo, Lin, and Christiani (2014), Li, Hedmer, Wojdacz, Hossain, et al. (2015), and Jiunn-Liang, Yu-Jung, Guan-Cen, I-Lun, and Hsiu-Ling (2017) assessed a longitudinal study of a cohort of cumulative welding fume-exposed boilermakers, a respirable dust-exposed group of Swedish welders, and metal exposure group of Central Taiwan workers. In the three groups, they observed telomere shortening in (1) peripheral blood leukocytes (PBL) in short-term-exposed boilermakers as opposed to workers who experienced extended exposures, (2) whole-blood of Swedish welders as analyzed by real-time quantitative polymerase chain reaction (qPCR), and (3) whole-blood lymphocytes of Taiwan workers as analyzed by southern blotting analysis, respectively (Jiunn-Liang et al., 2017; Li et al., 2015; Wong et al., 2014). After evaluating telomere length and changes in DNA methylation after welding fume exposure, Li et al. (2015) reported shorter telomere length in whole blood of Swedish welders as analyzed by qPCR. Because shorter telomeres in blood are associated with numerous cancers, this suggests a possible carcinogenic mechanism related to welding fume exposure. Importantly, augmented risk of lung cancer is also linked with elongated telomeres (Hosgood III et al., 2009; Lan, Cawthon, Gao, et al., 2013; Seow, Cawthon, Purdue, et al., 2014; Shen, Cawthon, Rothman, et al., 2011). Another possible cause of initiation of tumorigenesis in cells with shorter telomeres could be chromosomal instability resulting in specific gene mutation, thereby blocking senescence and apoptosis pathways. However, cells with elongated telomeres tend to have a longer lifespan, which can divide continuously and possibly inhibit senescence and apoptosis pathways, resulting in the occurrence of more somatic cells mutations (Li et al., 2015) and suggesting that both long and short telomeres may elevate the risk of tumorigenesis.

In our previous laboratory studies in which we evaluated telomere length homeostasis and epigenetic changes (DNA methylation) after exposure to different welding fumes in an animal model, no significant changes were observed when comparing DNA methylation in isolated PBMCs in the welding fume exposed and control groups (Shoeb, Joseph, Kodali, et al., 2017). However, isolated PBMCs from rats exposed to a cytotoxic and highly water-soluble stainless-steel welding fume had significantly increased telomere length ratios as determined by qPCR at 1- and 30-days post exposure as compared to the control groups (Shoeb, Kodali, Farris, et al., 2017). Also, this stainless-steel welding fume induced an elevation in oxidant production (ROS, P-HNE) in the PBMCs, indicating that the change in telomere length could be related to oxidative stress. du Plessis, Laubscher, Jooste, et al. (2010) previously reported surges of 87% and 96% in ROS production and lipid

peroxidation levels, respectively, in PBMCs isolated from workers exposed to welding fume compared to non-exposed control workers.

Both acute (metal fume fever, transient lung function changes) and chronic (bronchitis, cancer) welding fume-induced pulmonary effects are well documented (Antonini, Lewis, Roberts, & Whaley, 2003) as compared to its non-pulmonary effects, e.g., in the central nervous system. Welders also encountered other hazards, including intense heat and harmful UV radiation (Falcone & Zeidler-Erdely, 2019). Welders exposed to UV radiation have been observed to develop ocular melanoma, head and neck erythema (Antonini, 2014; Gallagher & Lee, 2006; Guha et al., 2017). Dysfunctional telomeres have been observed after UVB or sunlight exposure in both humans and mice (Ikeda, Aida, Hatamochiet, et al., 2014; Stout & Blasco, 2013), and these have been associated with increased risk of skin cancer (Armanios & Blackburn, 2012; DiGiovanna & Kraemer, 2012). Evidence also suggests that various neurological conditions and alteration of neuroinflammatory mediators can result from welding fume exposure, likely due to accumulation of welding fume-associated Mn in specific regions of the brain (Li, Zhang, Lu, Wu, & Zheng, 2004; Racette, Criswell, Lundin, et al., 2012; Racette, Searles Nielsen, & Criswell, 2017; Sriram et al., 2010; van der Mark, Vermeulen, Nijssen, et al., 2015). It is well documented in epidemiological studies that welders may be more susceptible to the development neurological dysfunction compared to non-welders (Racette et al., 2012).

Using an experimental animal model, we have assessed a possible association of welding fume-induced telomere alteration and neurodegeneration. Telomere length is regulated and maintained by shelterin proteins and its alteration is primarily due to amplified oxidative stress and telomerase activity. Double stranded shelterin proteins, TRF1, and TRF2, are the core for telomere protection and regulation. TRF1 is inversely proportional to telomere length. In other words, Trf1 negatively regulates telomere length, whereas TRF2 prevents chromosomal fusion and mutations (Shoeb et al., 2020). In our study to investigate the association between telomere length homeostasis and neurodegeneration, rats were exposed by inhalation to stainless steel welding fumes (20 mg/m3 × 3 h/d × 4 d/wk. × 5 wk) or filtered air (control). Telomere length, DNA-methylation, gene expression of TRF1, TRF2, ATM, and APP, protein expression of p-Tau, α-synuclein, and presenilin 1 and 2 were assessed in brain tissue at 12 weeks after welding fume exposure ended. We observed increased telomere length with no change in TERT expression in brain. We observed, significantly downregulated shelterin component TRF1 and TRF2 and increased expression of neurodegeneration markers, such as p-Tau, presenilin 1–2 and α-synuclein proteins, in brain tissue from the welding fumes-exposed animals as compared to air-control. Our observations suggested: (1) elongated telomere length and epigenetic alteration after welding fume exposure in rat brain is telomerase (TERT)-independent, (2) welding fume inhalation may cause increased telomere length and expression of neurodegeneration markers in rat brain through downregulation of TRF1 and TRF2, and (3) telomere length alteration and altered markers of neurodegeneration could be the due to translocation of potentially neurotoxic metals to the central nervous system (CNS) after welding fumes exposure; however, more region-specific studies are required to understand in-depth the correlation between telomere alteration and neurodegeneration after welding fumes exposures. To our knowledge, ours is the first study, using an animal exposure model that mimics an

occupational setting, to examine the association between welding fume inhalation and its possible correlation with telomere length, epigenetic alterations, and markers of neurodegeneration (Shoeb et al., 2020).

Furthermore, as the name indicates, shelterin proteins shield telomeres from incidences of unwanted DDR. One study conducted to understand the role of individual shelterin proteins involved in DDR and DNA repair pathways suggested that disruption in the specific shelterin subunit may lead to telomere dysfunction (Van Ly, Low, & Frölich, 2018) (e.g. inhibition or deletion of TRF1 may cause elongated telomere length). Therefore, another possible mechanism for telomere elongation in brain tissue after welding fume exposure may involve the downregulation of TRF1 (Shoeb et al., 2020). Importantly, depletion or deletion of TRF2 initiate genomic instability and tumorigenesis (Nera, Huang, Lai, & Xu, 2015) through activation of ATM kinase at telomeres, and subsequently may result in chromosomal fusion (Denchi & de Lange, 2007; Smogorzewska, Karlseder, Holtgreve-Grez, Jauch, & de Lange, 2002). Significantly increased ATM and decreased TRF2 were observed after welding fume exposure in vivo (Shoeb et al., 2020). However, under normal condition, activation of ATM kinase is inhibited by TRF2 (Denchi & de Lange, 2007). Our animal model may suggest that workers exposed to welding fumes may potentially develop epigenetic modification through activation of ATM-dependent DDR machinery and dysregulation of shelterin subunits TRF1 and TRF2 potentially contributing to adverse neurological effects. Consequently, additional laboratory studies are needed to evaluate a possible mechanistic and in-depth association between welding fume-induced non-pulmonary effects.

4.2. Silica industry

Approximately 2.3 million workers in the United States and several millions more globally are employed in different occupational sectors, such as mining, sand blasting, tunneling, silica milling, construction and hydraulic fracking and are potentially exposed to significant levels of crystalline silica (Esswein, Breitenstein, Snawder, et al., 2013; Radnoff, Todor, & Beach, 2014). The recommended exposure limit (REL) for crystalline silica as established by The National Institute for Occupational Safety and Health (NIOSH) is 0.05 mg/m^3 (Linch, Miller, Althouse, Groce, & Hale, 1998; NIOSH, 2002, https://www.cdc.gov/niosh/docs/2002-129/default.html). Because workers are often exposed to levels of dust above the recommended REL, they can develop a number of adverse health effects, such as lung fibrosis (Mazurek, Schleiff, Wood, Hendricks, & Weston, 2015), silicosis (Castranova & Vallyathan, 2000), cardiopulmonary dysfunction (Guo, Shi, et al., 2016), bronchitis (Merget, Bauer, Kupper, et al., 2002), tuberculosis (Rees & Murray, 2007), systemic sclerosis, rheumatoid arthritis (Rangel-Moreno, Hartson, Navarro, et al., 2006), chronic renal disease (Vupputuri, Parks, Nylander-French, et al., 2012) and lung cancer (Guha et al., 2011; IARC – International Agency for Research on Cancer, 1997).

IARC has categorized silica as a group I carcinogen, suggesting that inhalation of crystalline silica in an occupational setting is carcinogenic to humans (Guha et al., 2011, IARC – International Agency for Research on Cancer, 1997). However, silica-induced carcinogenic mechanisms are largely unknown. Silica has been shown in toxicology studies to be

cytotoxic (Antonini, McCloud, & Reasor, 1994; Fubini & Hubbard, 2003; Hamilton Jr., Thakur, & Holian, 2008) and reside longer in the lungs, leading to lung damage (Castranova, Porter, Millecchia, et al., 2002; Porter, Ye, Ma, et al., 2002) and alteration in telomere length and its regulatory protein expression (Shoeb, Joseph, et al., 2017; Shoeb, Mustafa, & Joseph, 2019). In an idiopathic pulmonary fibrotic patient, significant mutations affecting telomere length and function have been observed (Armanios & Blackburn, 2012; Armanios, Chen, Cogan, et al., 2007). Populations with genetically inherited shorter telomeres are more likely to develop idiopathic pulmonary fibrosis (Armanios, 2012), and the ratio of telomere shortening depended on their sex, male versus female (2:1) (Raghu, Weycker, Edelsberg, Bradford, & Oster, 2006). The phenomenon of diseases, such as pulmonary fibrosis, occurring due to dysfunctional telomeres and shelterin proteins are called telomere syndromes. As evident from previous laboratory studies, induction of pulmonary toxicity has been observed at 3, 6, and 12 weeks after short-term silica inhalation exposure (Umbright, Sellamuthu, & Roberts, 2017), and pulmonary fibrosis and its marker, α-SMA, were observed only after 12 weeks of silica inhalation in vivo (Shoeb et al., 2019). Telomerase maintains telomere length by specialized RNA template for telomere repeat addition. Elevated telomerase activity could result in increased telomere length, and mutations in TERT and TERC are risk factors for pulmonary fibrosis (Armanios et al., 2007; Hoffman et al., 2016). Elongated telomere length and elevated TERT gene expression as analyzed by qPCR have been observed in lung tissue at 4 and 32 weeks after a 5-d silica exposure compared to air controls in vivo (Shoeb, Kodali, et al., 2017). One possible explanation for the increase in telomere length in the lung tissue at these time points may be due to elevated telomerase activity which is dependent on the expression of TERT. Uncapping and hyperextension of telomeres have been reported due to the activation of DDR (Denchi & de Lange, 2007; Guo, Deng, Lin, et al., 2007), and its repression is regulated by shelterin proteins at telomeres (Shoeb et al., 2019). Tel2-interacting proteins 1 and 2 (TTI1) and (TTI2) are key regulators of DDR signaling. Thus, our finding suggests that destabilization of TTI2 after silica inhalation could be the reason for activation of DDR machinery. Furthermore, it is known that the regulator of telomere length-1 (RTEL1) protein preserves T-Loop structure of telomeres by unwinding telomeric G4 DNA. However, decreases in RTEL1 expression in lung tissue of rats were observed in the 5-d silica exposure regimen of the laboratory study (Shoeb, Kodali, et al., 2017), and also after 3, 6, and 12 weeks of silica exposure as compared to air control, suggesting the fragility of the telomere due to dysfunctional DDR machinery (TTI2) and altered RTEL1 (Shoeb et al., 2019). One of the functions of telomeres is to prevent the stimulation of the DDR by shielding the end of chromosomes from being identified as DNA strand breaks (Lazzerini-Denchi & Sfeir, 2016). Interestingly, silica exposure-initiated lung fibrosis (Umbright et al., 2017) and DNA damage (Shoeb et al., 2019) that progressed gradually over time in the lung tissue of the silica-exposed group as observed by the presence of γH2AX positive cells (Shoeb et al., 2019).

In previous studies using mice with elongated telomere, less metabolic aging and longer lifespans were observed. On the other hand, shorter lifespans and age-related pathologies have been demonstrated in telomere-deficient mice (Muñoz-Lorente, Cano-Martin, & Blasco, 2019). Generation of fragile telomeres as a result of dysfunctional shelterin

components can initiate cancer progression. Inhibition or inactivation of POT1 could result in the accumulation of increased DDR and telomere fusion (Denchi & de Lange, 2007; Hockemeyer, Daniels, Takai, & de Lange, 2006; Hockemeyer, Palm, Else, et al., 2007; Hockemeyer, Sfeir, Shay, Wright, & de Lange, 2005). In our studies, we observed inactivation of POT1 likely due to initiation of DDR (TTI2) at an early time point and progression until week 12 (γH2AX, and α-SMA) after silica inhalation (Shoeb et al., 2019). Silica-induced transformation of epithelial cells to mesenchymal cells, including epithelial mesenchymal transition (EMT) (Wynn & Ramalingam, 2012) could result in lung injury and initiation of pulmonary fibrosis and is characterized by the induction of telomerase in epithelial cells and fibroblasts (Liu, Ullenbruch, Young Choi, et al., 2013), and TERT and α-SMA expression in lung tissue (Shoeb et al., 2019; Shoeb, Kodali, et al., 2017).

DNA damage can also occur due to dysfunctional shelterin complex subunits resulting in dsDNA and ssDNA break at the telomeres (Shoeb et al., 2019). To the best of our knowledge, there are surprisingly no previous studies showing shelterin dysregulation in human or animals after silica exposure. We investigated the effect of silica inhalation on shelterin components in lung tissue in vivo. Again, we observed that ssDNA protein, POT1, and the protein which bridges dd- and ssDNA, TIN2, were downregulated initially. Later, at 6 weeks after silica exposure, almost all the shelterin components were altered except RAP1. Finally, at week 12 after inhalation, the entire shelterin complex became dysfunctional. Other than the bridge formation between POT1-TPP1 and TRF2-TRF1, TIN2 also regulates telomerase recruitment. Thus, its depletion may result in reduced levels of telomerase recruitment, thereby causing a dysfunctional shelterin complex and activation of DNA damage signaling and telomere instability (Shoeb et al., 2019).

Furthermore, RAP1, a shelterin subunit attached with TRF2 at dsDNA, is involved in repression of proteins and in initiation of T loop cleavage, NHEJ and HR for e.g. PARP1 and SLX4, thus, preventing catastrophic telomere loss and the generation of telomere-free chromosomal fusions (Rai, Chen, Lei, & Chang, 2016). Because RAP1-TRF2 stabilize the telomeric dsDNA–ssDNA junction by blocking HR (Lazzerini-Denchi & Sfeir, 2016), stable RAP1 was observed at early time points after silica exposure but was significantly downregulated after sub-chronic time points after silica exposure, suggesting the destabilization of ds-ssDNA bridge, and thus a dysfunctional shelterin complex (Shoeb et al., 2019). Based on the findings by our group, analysis of telomere length and its governing proteins after silica exposure may serve as potential biomarkers in the assessment of toxicological outcomes and also contribution to elucidate the mechanisms of disease development such as tumorigenesis, carcinogenesis, and pulmonary fibrosis.

4.3. Other industries

Due to exposure to complex mixtures of toxic substances, workers in the rubber industry have been observed to be more susceptible to adverse health effects, such as respiratory (Robichova, Slamenova, Gabelova, et al., 2004), cardiovascular (Gustavsson, Hogstedt, & Holmberg, 1986), and several types of cancer (de Vocht, Sobala, Wilczynska, et al., 2009; Vlaanderen, Taeger, Wellman, et al., 2013). Because of undetermined permissible exposure limits (PELs) by the Occupational Safety and Health Administration (OSHA) or RELs by

NIOSH, it is difficult to elucidate the effects of a specific chemical resulting in excess fatalities of workers in the rubber industry (SPECIAL NIOSH HAZARD REVIEW, 1993; https://www.cdc.gov/niosh/docs/93–106/default.html). Hundreds of potentially toxic chemicals (e.g., N-nitrosamines, carbon disulphide (CS_2), PAH, and toluidines) are released as products and byproducts from the production of rubber and may play an important role in the generation of oxidative stress, DNA damage, and DNA adduct formation (Li, Jonsson, Lindh, et al., 2011). Currently, there are few studies correlating exposure of the chemicals associated with rubber production and telomere alteration. Recently Li et al. (2011), performed a cross-sectional study on a Swedish worker population in the rubber industry in order to establish a relation between chemicals exposure from rubber production and telomere length. It was concluded that exposure to N-nitrosamines was associated with reduced telomere length in peripheral blood samples as analyzed by qPCR in the workers. The association of telomere length alteration and occupational exposure to polyaromatic hydrocarbons (PAHs) liberated during addition of crumb rubber to asphalt or crumb rubber modified asphalt (CRM asphalt) has been examined (Xu, Lindh, Jönssonet, et al., 2018). CRM asphalt is utilized for road paving for the reduction of traffic sound as compared to petroleum-derived asphalt. Xu et al. (2018), assessed the potential effects of exposure to PAHs generated from both CRM and petroleum-derived asphalt by measuring PAH metabolites in urine, mitochondrial DNA copy number (mtDNAcn), and telomere length in peripheral blood. Workers exposed to both asphalts experienced oxidative stress, elevated PAH metabolites, and altered mtDNAcn. However, no effect was observed after short term PAH exposure on telomere length between occupational and control groups.

Coal is an important source for electricity worldwide, and occupational exposure to coal mine dust inhalation can result in fibrosis, silicosis, asbestosis, as well as lung and liver cancer (Howarth, Ingraffea, & Engelder, 2011; IARC – International Agency for Research on Cancer, 1997; Jenkins, Christian, Mueller, & Robbins, 2013). The guanine rich 3′ overhang of the telomere is most susceptible to oxidative damage, therefore, a possible mechanism by which coal dust induces DNA damage could be due to elevated oxidative stress. Recently, de Souza et al. (2018) observed an association between shorter telomere length and DNA methylation in peripheral blood samples as analyzed by qPCR and high-performance liquid chromatography (HPLC) in 55 workers exposed to coal dust and 27 non-exposed individuals. Due to the complex chemical nature of coal dusts, it is difficult to classify any specific chemical-induced genotoxicity and genomic instability, indicating that reduced telomere length and elevated DNA methylation in coal workers could be due to increased oxidative damage resulting from exposure to inorganic elements present in coal.

Chronic exposure to lead in the workplace has been considered a risk factors for cardiovascular disease and cancer (Schober, Mirel, Graubard, Brody, & Flegal, 2006). Occupational exposure of lead exerts different effects depending on the duration and level of exposure (i.e., long-term exposure can result in telomere shortening by inhibiting telomerase activity, whereas low level of exposure could impact the cardiovascular system) (Cui, Tang, & Huang, 2002; He, Chen, Dai, Li, & Zhu, 2018; Wu, Liu, et al., 2012). Cardiac myocyte apoptosis and downregulation of TRF2 expression through induction of the DNA damage-regulated activation of the checkpoint kinase, CHK2, was revealed in heart patients (Serrano & Andrés, 2004). Toxic effects of lead could possibly due to its longer occupancy time in

bones (approximately 11–90 years) and its nearly month-long half-life in blood. Lead is widely used in battery manufacturing, architectural metal, power cables, sailboat keels, among many other products (He et al., 2018). Despite the high level of DNA damage after lead exposure, (Wu, Takai, & de Lange, 2012), first observed shorter telomere length in peripheral white blood cells by qPCR in occupationally exposed lead workers in a Chinese battery plant. Also, there is growing evidence that suggest an increased cardiovascular mortality after lead exposure. Pawlas, Płachetka, Kozłowska, et al. (2016) also observed shorter telomere length in whole blood genomic DNA as analyzed by qPCR in 334 male lead smelters compared to the 60 male workers control group. Therefore, lead-induced telomere shorting could result in accelerating aging which in turn contributes to cardiovascular dysfunction.

Like lead exposure, shorter telomeres were observed in recovered buccal cell DNA from automobile workers compared with unexposed controls. Exposure of workers to different genotoxic and carcinogenic chemicals (e.g., petrochemicals and other vapors) in the automobile sector have resulted in the activation of DNA damage through stimulation of oxidative stress and deficiency of the antioxidant pool (Eshkoor et al., 2012). Therefore, workers in in automobile occupation may be more susceptible to induction of oxidative DNA damage-mediated accelerated aging and telomere shortening. More studies are needed to evaluate additional possible mechanisms and relationship between lead and automobile-induced genotoxicity and telomere alteration.

5. Conclusion

Evaluation of telomere length, its regulatory proteins, DDR, and analysis of epigenetic modifications, could be utilized as potential biological endpoints in the assessment of understanding the mechanisms and development of disease conditions after different occupational exposures. Telomere length, telomerase activity (TERT and TERC), shelterin complex proteins, ATM, ATR kinases, DNA damage foci also could be potential biological factors that provide information about the responses induced by different occupational exposures. Furthermore, examining telomere length at birth, before an individual joins the workforce, and during active employment will provide information of changes in telomere length with increasing age and may help to determine telomere length alterations in response to occupational exposures, thereby providing elucidation of possible telomere dynamics and disease prognosis. Telomere alteration has been shown to be related to increased risk of diabetes, cardiovascular diseases, dementia, and cancer as a decrease in mtDNAcn is one of the hallmarks of telomere dysfunction in cancer (Prigione, Fauler, Lurz, Lehrach, & Adjaye, 2010). Occupational exposures can also result in epigenetic modifications, including DNA methylation, histone modifications and microRNA regulation, and play an important role in telomere maintenance. Elongated telomeres and telomeric recombination were reported in DNA methyltransferase-deficient mammalian cells compared to wild-type control cells, suggesting the significance of epigenetic factors in maintaining telomere integrity (Zhang, Lin, Funk, & Hou, 2013). Compared to the rest of the DNA, telomeric DNA cannot repair (ssDNA and dsDNA) itself efficiently, resulting in alteration of its homeostasis during the cell cycle. However, telomeric sequence and its regulatory proteins (e.g., shelterin subunit TRF2) repair dsDNA break through mechanism known as NHEJ (Denchi & de Lange,

2007). Therefore, TRF2 could be a vital biological endpoint to analyze for occupational exposure. For example, induced DNA damage as inactivated by TRF2 may lead telomere attrition and activation of CHK2 signaling (Serrano & Andrés, 2004), possibly resulting in detrimental consequences to workers' health.

Dysfunctional telomeres can lead to activation of damaged DNA and other molecular cascades, such as activation of p53 pathways through phosphorylation and activation of ATM and CHK2. Being a guardian of the genome, p53 can provoke the onset of cellular senescence, and sometimes apoptosis, a known anti-tumorigenic mechanism. On the other hand, dysfunctional telomeres related to p53 mutation or p53 deficiency may increase the risk of tumorigenesis which is considered as a pro-tumorigenic mechanism. Both elongated and short telomeres are linked to lung and kidney cancer (Hou, Zhang, Gawron, et al., 2012). Analysis of only telomere length will not be an adequate biomarker/endpoint to understand the development of disease after occupational exposures. Therefore, the current challenge for investigators is to evaluate additional biological endpoints to analyze not only telomere length, but its regulatory proteins, and DDR to further understand mechanisms and elucidate early occupational pathologies and their potential implications on worker's health. Because telomere ssDNA is rich in guanine residues and are more susceptible to oxidative damage (Fouquerel et al., 2016; Houben et al., 2008; Kawanishi & Oikawa, 2004), quantification of 8-hydroxy-2-deoxyguanosine (8-oxodG) at the telomere could be an important guide to understand telomere alteration. Also, proteins associated with ALT pathways, such as α-thalassemia/mental retardation syndrome X-linked protein (ATRX) and death domain-associated protein (DAXX) mutation, have been observed in ALT positive cancers (Heaphy, de Wilde, Jiao, et al., 2011). Therefore, investigation of underlying mechanisms resulting in dysregulation of DAXX/ATRX proteins, identification and quantification of TERRA transcription at the sub-telomeric region, telomere transcription factor such as SNAIL1, and the factors influencing telomerase reactivation, such as changes in TERT expression and amplification of TERT and TERC (Barthel et al., 2017), after occupational exposures could be a promising approach to address and comprehend these complications.

Acknowledgments

This study was supported by funding from The National Institute for Occupational Safety and Health-National Occupational research Agenda Project # 9390DT4.

Abbreviations:

DDR	DNA damage response
ssDNA	Single strand DNA
dsDNA	Double strand DNA
TERT	Telomerase reverse transcriptase
TERC	Telomerase RNA component
ALT	Alternative lengthening of telomeres

TRF1 and TRF2	Telomere repeat factors 1 and 2
TIN2	Trf1-interacting protein 2
TPP1	Tripeptidyl peptidase 1
POT1	Protection of telomere 1
RAP1	Repressor/activator protein 1
ATR	Ataxia telangiectasia and Rad3-related
ATM	Ataxia telangiectasia-mutated

References

Adnot S, Amsellem V, Boyer L, et al. (2015). Telomere dysfunction and cell senescence in chronic lung diseases: Therapeutic potential. Pharmacology & Therapeutics 153, 125–134. [PubMed: 26096607]

Ambroise D, Wild P, & Moulin JJ (2006). Update of a meta-analysis on lung cancer and welding. Scandinavian Journal of Work, Environment & Health 32, 22–31.

Antonini JM (2014). Health effects associated with welding. In Bassim N (Ed.), Comprehensive materials processing 8 (pp. 49–70). Oxford, UK: Elsevier Ltd.

Antonini JM, Lewis AB, Roberts JR, & Whaley DA (2003). Pulmonary effects of welding fumes: Review of worker and experimental animal studies. American Journal of Industrial Medicine 43(4), 350–360. [PubMed: 12645092]

Antonini JM, McCloud CM, & Reasor MJ (1994). Silica toxicity in rat lung: Attenuation by amiodarone-induced pulmonary phospholipidosis. Environmental Health Perspectives 102, 372–378. [PubMed: 7925177]

Armanios M (2012). Telomerase and idiopathic pulmonary fibrosis. Mutation Research730, 52–58.

Armanios M, & Blackburn EH (2012). The telomere syndromes. Nature Reviews.Genetics 13, 693–704.

Armanios MY, Chen JJ, Cogan JD, et al. (2007). Telomerase mutations in families with idiopathic pulmonary fibrosis. The New England Journal of Medicine 356, 1317–1326. [PubMed: 17392301]

Attwooll CL, Akpinar M, & Petrini JH (2009). The Mre11 complex and the response to dysfunctional telomeres. Molecular and Cellular Biology 29, 5540–5551. [PubMed: 19667076]

Azzalin CM, Reichenbach P, Khoriauli L, Giulotto E, & Lingner J (2007). Telomeric repeat containing RNA and RNA surveillance factors at mammalian chromosome ends. Science 318, 798–801. [PubMed: 17916692]

Baker DJ, Childs BG, Durik M, et al. (2016). Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189. [PubMed: 26840489]

Baker DJ, Wijshake T, Tchkonia T, et al. (2011). Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236. [PubMed: 22048312]

Barthel FP, Wei W, Tang M, et al. (2017). Systematic analysis of telomere length and somatic alterations in 31 cancer types. Nature Genetics 49(3), 349–357. [PubMed: 28135248]

Blackburn EH (1990). Telomeres and their synthesis. Science 249, 489–490. [PubMed: 2200120]

Blackburn EH, Greider CW, Henderson E, et al. (1989). Recognition and elongation of telomeres by telomerase. Genome 31, 553–560. [PubMed: 2698831]

Blasco MA (2005). Telomeres and human disease: Ageing, cancer and beyond. NatureReviews. Genetics 6, 611–622. [PubMed: 16136653]

Bryan TM, Englezou A, Dalla-Pozza L, Dunham MA, & Reddel RR (1997). Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor derived cell lines. Nature Medicine 3, 1271–1274.

Cahu J, Bustany S, & Sola B (2012). Senescence-associated secretory phenotype favors the emergence of cancer stem-like cells. Cell Death Dis. 3, (12): e446. [PubMed: 23254289]

Castranova V, Porter D, Millecchia L, et al. (2002). Effect of inhaled crystalline silica in a rat model: Time course of pulmonary reactions. Mol. Cell. Biochem 234, 235, 177 184. [PubMed: 12162431]

Castranova V, & Vallyathan V (2000). Silicosis and coal workers' pneumoconiosis. Environmental Health Perspectives 108, 675–684.

Celli GB, & de Lange T (2005). DNA processing is not required for ATM-mediated telomere damage response after TRF2 deletion. Nat. Cell Biol 7, 712–718. [PubMed: 15968270]

Cesare AJ, Kaul Z, Cohen SB, et al. (2009). Spontaneous occurrence of telomeric DNA damage response in the absence of chromosome fusions. Nature Structural & Molecular Biology 16, 1244–1251.

Cesare AJ, & Reddel RR (2010). Alternative lengthening of telomeres: Models, mechanisms and implications. Nature Reviews. Genetics 11, 319–330.

Chen YA, Shen YL, Hsia HY, et al. (2017). Extrachromosomal telomere repeat DNA is linked to ALT development via cGASSTING DNA sensing pathway. Nature Structural & Molecular Biology 24, 1124–1131.

Childs BG, Baker DJ, Wijshake T, et al. (2016). Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science 354, 472–477. [PubMed: 27789842]

Churikov D, & Price CM (2008). Pot1 and cell cycle progression cooperate in telomere length regulation. Nature Structural & Molecular Biology 15, 79–84.

Conomos D, Pickett HA, & Reddel RR (2013). Alternative lengthening of telomeres: Remodeling the telomere architecture. Frontiers in Oncology 3, 27. [PubMed: 23429284]

Cui QH, Tang CC, & Huang YG (2002). Effects of lead and selenium on telomere binding protein rap1p, telomerase and telomeric DNA in Saccharomyces cerevisiae. Acta Biochimica et Biophysica Sinica 34, :240–4. [PubMed: 12007004]

Cusanelli E, Romero CA, & Chartrand P (2013). Telomeric noncoding RNA TERRA is induced by telomere shortening to nucleate telomerase molecules at short telomeres. Molecular Cell 51, 780–791. [PubMed: 24074956]

Denchi EL, & de Lange T (2007). Protection of telomeres through independent control of ATM and ATR by TRF2 and POT1. Nature 448, 1068–1071. [PubMed: 17687332]

Deng Y, Guo X, Ferguson DO, & Chang S (2009). Multiple roles for MRE11 at uncapped telomeres. Nature 460, 914–918. [PubMed: 19633651]

van Deursen JM (2014). The role of senescent cells in ageing. Nature 509, 439–446. [PubMed: 24848057]

DiGiovanna JJ, & Kraemer KH (2012). Shining a light on xeroderma pigmentosum. The Journal of Investigative Dermatology 132, 785–796. [PubMed: 22217736]

Dimitrova N, & de Lange T (2009). Cell cycle dependent role of MRN at dysfunctional telomeres: ATM signaling-dependent induction of NHEJ in G1 and resection-mediated inhibition of NHEJ in G2. Molecular and Cellular Biology 29, 5552–5563. [PubMed: 19667071]

Ding Z, Wu C-J, Jaskelioff M, et al. (2012). Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases. Cell 148, 896–907. [PubMed: 22341455]

Doksani Y, & de Lange T (2014). The role of double-Strand break repair pathways at functional and dysfunctional telomeres. Cold Spring Harbor Perspectives in Biology 6(12) a016576. [PubMed: 25228584]

Eshkoor SA, et al. (2012). Association between telomere shortening and ageing during occupational exposure. J Med Biochem 31, 211–216.

Esswein EJ, Breitenstein M, Snawder J, et al. (2013). Occupational exposures to respirable crystalline silica during hydraulic fracturing. Journal of Occupational and Environmental Hygiene 10, 347–356. [PubMed: 23679563]

Falcone LM, & Zeidler-Erdely PC (2019). Skin cancer and welding. Clinical and Experimental Dermatology 44(2), 130–134. [PubMed: 30280417]

Fitzpatrick AL, Kronmal RA, Gardner JP, et al. (2007). Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. American Journal of Epidemiology 165, 14–21. [PubMed: 17043079]

Fouquerel E, Lormand J, Bose A, et al. (2016). Oxidative guanine base damage regulates human telomerase activity. Nature Structural & Molecular Biology 23(12), 1092–1100.

Fubini B, & Hubbard A (2003). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. Free Radical Biology & Medicine 34, 1507–1516. [PubMed: 12788471]

Gallagher RP, & Lee TK (2006). Adverse effects of ultraviolet radiation: A brief review. Progress in Biophysics and Molecular Biology 92, 119–131. [PubMed: 16580054]

Gilson E, & Geli V (2007). How telomeres are replicated. Nat Rev Mol Cell Biol 8,825–838. [PubMed: 17885666]

Giraud-Panis MJ, Teixeira MT, Geli V, & Gilson E (2010). CST meets shelterin to keep telomeres in check. Molecular Cell 39, 665–676. [PubMed: 20832719]

Gocha AR, Harris J, & Groden J (2013). Alternative mechanisms of telomere lengthening: Permissive mutations, DNA repair proteins and tumorigenic progression. Mutation Research 743(744), 142–150. [PubMed: 23219603]

Gong Y, & de Lange T (2010). A Shld1-controlled POT1a provides support for repression of ATR signaling at telomeres through RPA exclusion. Molecular Cell 40, 377–387. [PubMed: 21070964]

Grach A (2013). Telomere shortening mechanisms. The Mechanisms of DNA Replication.. 10.5772/55244.

Greider CW (1991). Telomeres. Curr. Opin. Cell Biol 3, 444–451. [PubMed: 1892656]

Greider CW (1996). Telomere length regulation. Annual Review of Biochemistry 65,337–365.

Greider CW, & Blackburn EH (1985). Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell 43, 405–413. [PubMed: 3907856]

Greider CW, & Blackburn EH (1989). A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. Nature 337, 331–337. [PubMed: 2463488]

Griffith JD, Comeau L, Rosenfield S, et al. (1999). Mammalian telomeres end in a large duplex loop. Cell 97, 503–514. [PubMed: 10338214]

Guha N, Loomis D, Guyton KZ, et al. (2017). Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. The Lancet Oncology 18(5), 581–582. [PubMed: 28408286]

Guha N, Straif K, & Benbrahim-Tallaa L (2011). The IARC monographs on the carcinogenicity of crystalline silica. La Medicina del Lavoro 102(4), 310–320. [PubMed: 21834268]

Günes C, Wezel F, Southgate J, & Bolenz C (2018). Implications of TERT promoter mutations and telomerase activity in urothelial carcinogenesis. Nature Reviews. Urology 15, 386–393. [PubMed: 29599449]

Guo J, Shi T, Cui X, et al. (2016). Effects of silica exposure on the cardiac and renal inflammatory and fibrotic response and the antagonistic role of interleukin-1 beta in C57BL/6 mice. Archives of Toxicology 90, 247–258. [PubMed: 25388157]

Guo X, Deng Y, Lin Y, et al. (2007). Dysfunctional telomeres activate an ATM-ATR-dependent DNA damage response to suppress tumorigenesis. The EMBO Journal 26(22), 4709–4719. [PubMed: 17948054]

Gustavsson P, Hogstedt C, & Holmberg B (1986). Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scandinavian Journal of Work, Environment & Health 12(6), 538–544.

Haber JE (1999). Sir-Ku-itous routes to make ends meet. Cell 97, 829–832. [PubMed: 10399911]

Hamilton RF Jr., Thakur SA, & Holian A (2008). Silica binding and toxicity in alveolar macrophages. Free Radical Biology & Medicine 44, 1246–1258. [PubMed: 18226603]

Hansen KS, Lauritsen JM, & Skytthe A (1996). Cancer incidence among mild steel and stainless-steel welders and other metal workers. American Journal of Industrial Medicine 30, 373–382. [PubMed: 8892541]

Hayflick L (1965). The limited in vitro lifetime of human diploid cell strains. Experimental Cell Research 37, 614–636. [PubMed: 14315085]

Hayflick L, & Moorhead PS (1961). The serial cultivation of human diploid cell strains. Experimental Cell Research 25, 585–621. [PubMed: 13905658]

He L, Chen Z, Dai B, Li G, & Zhu G (2018). Low-level lead exposure and cardiovascular disease: The roles of telomere shortening and lipid disturbance. The Journal of Toxicological Sciences 43(11), 623–630. [PubMed: 30404996]

Heaphy CM, de Wilde RF, Jiao YC, et al. (2011). Altered telomeres in tumors with ATRX and DAXX mutations. Science 333(6041), 425. [PubMed: 21719641]

Henson JD, Neumann AA, Yeager TR, & Reddel RR (2002). Alternative lengthening of telomeres in mammalian cells. Oncogene 21, 598–610. [PubMed: 11850785]

Hockemeyer D, Daniels JP, Takai H, & de Lange T (2006). Recent expansion of the telomeric complex in rodents: Two distinct POT1 proteins protect mouse telomeres. Cell 126, 63–77. [PubMed: 16839877]

Hockemeyer D, Palm W, Else T, et al. (2007). Telomere protection by mammalian Pot1 requires interaction with Tpp1. Nature Structural & Molecular Biology 14, 754–761.

Hockemeyer D, Sfeir AJ, Shay JW, Wright WE, & de Lange T (2005). POT1 protects telomeres from a transient DNA damage response and determines how human chromosomes end. The EMBO Journal 24, 2667–2678. [PubMed: 15973431]

Hoffman TW, et al. (2016). TINF2 gene mutation in a patient with pulmonary fibrosis. Case Rep Pulmonol 2016, 1310862.

Horn S, Figl A, Rachakonda PS, et al. (2013). TERT promoter mutations in familial and sporadic melanoma. Science, 22 339(6122), 959–961.

Hosgood HD III, Cawthon R, He X, et al. (2009). Genetic variation in telomere maintenance genes, telomere length, and lung cancer susceptibility. Lung Cancer 66(2), 157–161. [PubMed: 19285750]

Hou L, Zhang X, Gawron AJ, et al. (2012). Surrogate tissue telomere length and cancer risk: Shorter or longer. Cancer Letters 319, 130–135. [PubMed: 22269209]

Hou L, Zhang X, Wang D, et al. (2012). Environmental chemical exposures and human epigenetics. International Journal of Epidemiology 41, 79–105. [PubMed: 22253299]

Houben JM, Moonen HJ, van Schooten FJ, & Hageman GJ (2008). Telomere length assessment: Biomarker of chronic oxidative stress? Free Radical Biology & Medicine 1(44), 235–246.

Howarth RW, Ingraffea A, & Engelder T (2011). Natural gas: Should fracking stop? Nature 477, 271–275. [PubMed: 21921896]

Hu J, Sarah Hwang S, Liesa M, et al. (2012). Antitelomerase therapy provokes ALT and mitochondrial adaptive mechanisms in cancer. Cell 148, 651–663. [PubMed: 22341440]

IARC – International Agency for Research on Cancer (1997). Silica, some silicates, coal dust and para-aramid fibrils, IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans, Lyon 68. 528 On-line: http://monographs.iarc.fr/ENG/Monographs/vol68/mono68.pdf.

Ibfelt E, Bonde JP, & Hansen J (2010). Exposure to metal welding fume particles and risk for cardiovascular disease in Denmark: A prospective cohort study. Occupational and Environmental Medicine 67, 772–777. [PubMed: 20581417]

Ikeda H, Aida J, Hatamochiet A, et al. (2014). Quantitative fluorescence in situ hybridization measurement of telomere length in skin with/without sun exposure or actinic keratosis. Human Pathology 45, 473–480. [PubMed: 24411948]

International Agency for Research on Cancer (IARC) (2012a). Arsenic, metals, fibres, and dusts: A review of human carcinogens. Lyon. 100C, 526.

International Agency for Research on Cancer (IARC) (2012b). A review of human carcinogens: Chemical agents and related occupations. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 100F, 541–559.

Jafri MA, Ansari SA, Alqahtani MH, & Shay JW (2016). Roles of telomeres and telomerase in cancer, and advances in telomerase-targeted therapies. Genome Medicine 8, 69. [PubMed: 27323951]

Jenkins WD, Christian WJ, Mueller G, & Robbins KT (2013). Population cancer risks associated with coal mining: A systematic review. PLoS One 8 713–12.

Jiunn-Liang KO, Yu-Jung C, Guan-Cen L, I-Lun H, & Hsiu-Ling C (2017). The association of occupational metals exposure and oxidative damage, telomere shortening in fitness equipments manufacturing workers. Industrial Health 55(4), 345–353. [PubMed: 28420806]

Kawanishi S, & Oikawa S (2004). Mechanism of telomere shortening by oxidative stress. Annals of the New York Academy of Sciences 1019(1), 278–284. [PubMed: 15247029]

Kendzia B, Behrens T, Jockel KH, et al. (2013). Welding and lung cancer in a pooled analysis of case control studies. American Journal of Epidemiology 178, 1513–1525. [PubMed: 24052544]

Kim N, Piatyszek M, Prowse K, et al. (1994). Specific association of human telomerase activity with immortal cells and cancer. Science 266, 2011–2015. [PubMed: 7605428]

Lan Q, Cawthon R, Gao Y, et al. (2013). Longer telomere length in peripheral white blood cells is associated with risk of lung cancer and the rs2736100 (CLPTM1L-TERT) polymorphism in a prospective cohort study among women in China. PLoS One 8, (3): e59230. [PubMed: 23555636]

de Lange T (2005a). Shelterin: The protein complex that shapes and safeguards human telomeres. Genes & Development 19, 2100–2110. [PubMed: 16166375]

de Lange T (2005b). Telomere-related genome instability in cancer. Cold Spring Harbor Symposia on Quantitative Biology 70, 197–204. [PubMed: 16869754]

de Lange T (2010). How shelterin solves the telomere end-protection problem. Cold Spring Harbor Symposia on Quantitative Biology 75, 167–177. [PubMed: 21209389]

de Lange T (2018). Shelterin-mediated telomere protection. Annual Review of Genetics 52, 223–247.

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. [PubMed: 27165790]

Li GJ, Zhang LL, Lu L, Wu P, & Zheng W (2004). Occupational exposure to welding fume among welders: Alterations of manganese, iron, zinc, copper, and lead in body fluids and the oxidative stress status. Journal of Occupational and Environmental Medicine 46(3), 241–248. [PubMed: 15091287]

Li H, Hedmer M, Wojdacz T, Hossain MB, et al. (2015). Oxidative stress, telomere shortening, and DNA methylation in relation to Low-to-moderate occupational exposure to welding fumes. Environmental and Molecular Mutagenesis 56(8), 684–693. [PubMed: 26013103]

Li H, Jonsson BA, Lindh CH, et al. (2011). N-nitrosamines are associated with shorter telomere length. Scandinavian Journal of Work, Environment & Health 37, 316–324.

Linch KD, Miller WE, Althouse RB, Groce DW, & Hale JM (1998). Surveillance of respirable crystalline silica dust using OSHA compliance data (1979–1995). American Journal of Industrial Medicine 34, 547–558. [PubMed: 9816412]

Liu R, Zhang T, Zhu G, & Xing M (2018). Regulation of mutant TERT by BRAF V600E/ MAP kinase pathway through FOS/GABP in human cancer. Nature Communications 9, 579.

Liu T, Ullenbruch M, Young Choi Y, et al. (2013). Telomerase and telomere length in pulmonary fibrosis. American Journal of Respiratory Cell and Molecular Biology 49(2), 260–268. [PubMed: 23526226]

Londono-Vallejo JA, & Wellinger RJ (2012). Telomeres and telomerase dance to the rhythm of the cell cycle. Trends in Biochemical Sciences 37, 391–399. [PubMed: 22727244]

Lovejoy CA, Li W, Reisenweber S, et al. (2012). Loss of ATRX, genome instability, and an altered DNA damage response are hallmarks of the alternative lengthening of telomeres pathway. PLoS Genetics 8(7), e1002772. [PubMed: 22829774]

Lundblad V, & Blackburn EH (1993). An alternative pathway for yeast telomere maintenance rescues est1- senescence. Cell 73, 347–360. [PubMed: 8477448]

van der Mark M, Vermeulen R, Nijssen PC, et al. (2015). Occupational exposure to solvents, metals and welding fumes and risk of Parkinson's disease. Parkinsonism & Related Disorders 21(6), 635–639. [PubMed: 25903042]

Martin CJ, Guidotti TL, & Langard S (1997). Respiratory hazards of welding. Clinical Pulmonary Medicine 4, 194–204.

Mazurek JM, Schleiff PL, Wood JM, Hendricks SA, & Weston A (2015). Control centers for disease, and prevention. Notes from the field: Update: Silicosis mortality-United States, 1999–2013. Morb Mortal Wkly Reports 64, 653–654.

Merget R, Bauer T, Kupper HU, et al. (2002). Health hazards due to the inhalation of amorphous silica. Archives of Toxicology 75, 625–634. [PubMed: 11876495]

Meyerson M, Counter CM, Eaton EN, et al. (1997). hEST2, the putative human telomerase catalytic subunit gene, is up regulated in tumor cells and during immortalization. Cell 90, 785–795. [PubMed: 9288757]

Min J, Wright WE, & Shay JW (2017). Alternative lengthening of telomeres mediated by mitotic DNA synthesis engages break-induced replication processes. Molecular and Cellular Biology 37(20) e00226–17. [PubMed: 28760773]

Muller HJ (1938). The remaking of chromosomes. Collecting Net 13, 15.

Muñoz-Lorente MA, Cano-Martin AC, & Blasco MA (2019). Mice with hyper-long telomeres show less metabolic aging and longer lifespans. Nature Communications 10(1), 4723.

Nera B, Huang HS, Lai T, & Xu L (2015). Elevated levels of TRF2 induce telomeric ultrafine anaphase bridges and rapid telomere deletions. Nature Communications 6, 10132.

Neumann AA, Watson CM, Noble JR, et al. (2013). Alternative lengthening of telomeres in normal mammalian somatic cells. Genes & Development 27, 18–23. [PubMed: 23307865]

NIOSH (2002). Hazard review: Health effects of occupational exposures to respirable crystalline silica. US Department of Health and Human Services (NIOSH) Publication No. 2002–129. Retrieved from https://www.cdc.gov/niosh/docs/2002-129/default.html.

Oeseburg H, de Boer RA, van Gilst WH, & van der Harst P (2010). Telomere biology in healthy aging and disease. Pflügers Archiv 459(2), 259–268. [PubMed: 19756717]

Ogrodnik M, Miwa S, Tchkonia T, et al. (2017). Cellular senescence drives age-dependent hepatic steatosis. Nature Communications 8, 15691.

Olovnikov AM (1973). A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. Journal of Theoretical Biology 41, 181–190. [PubMed: 4754905]

Palm W, & de Lange T (2008). How shelterin protects mammalian telomeres. Annual Review of Genetics 42, 301–334.

Pawlas N, Płachetka A, Kozłowska A, et al. (2016). Telomere length, telomerase expression, and oxidative stress in lead smelters. Toxicology and Industrial Health 32(12), 1961–1970. [PubMed: 26381690]

du Plessis L, Laubscher P, Jooste J, et al. (2010). Flow cytometric analysis of the oxidative status in human peripheral blood mononuclear cells of workers exposed to welding fumes. Journal of Occupational and Environmental Hygiene 7, 367–374. [PubMed: 20397091]

Porter DW, Ye J, Ma J, et al. (2002). Time course of pulmonary response of rats to inhalation of crystalline silica: NF-kappa B activation, inflammation, cytokine production, and damage. Inhalation Toxicology 14, 349–367. [PubMed: 12028809]

Price CM, Boltz KA, Chaiken MF, et al. (2010). Evolution of CST function in telomere maintenance. Cell Cycle 9, 3157–3165. [PubMed: 20697207]

Prigione A, Fauler B, Lurz R, Lehrach H, & Adjaye J (2010). The senescence-related mitochondrial/oxidative stress pathway is repressed in human induced pluripotent stem cells. Stem Cells 28(4), 721–733. [PubMed: 20201066]

Racette BA (2014). Manganism in the 21st century: The Hanninen lecture. Neurotoxicology 45, 201–207. [PubMed: 24148923]

Racette BA, Criswell SR, Lundin JI, et al. (2012). Increased risk of parkinsonism associated with welding exposure. Neurotoxicology 33(5), 1356–1361. [PubMed: 22975422]

Racette BA, McGee-Minnich L, Moerlein SM, et al. (2001). Welding-related parkinsonism: Clinical features, treatment, and pathophysiology. Neurol 56, 8–13.

Racette BA, Searles Nielsen S, & Criswell SR (2017). Dose-dependent progression of parkinsonism in manganese-exposed welders. Neurology 88(4), 344–351. [PubMed: 28031394]

Radnoff D, Todor MS, & Beach J (2014). Occupational exposure to crystalline silica at Alberta work sites. Journal of Occupational and Environmental Hygiene 11, 557–570. [PubMed: 24479465]

Raghu G, Weycker D, Edelsberg J, Bradford WZ, & Oster G (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine 174, 810–816. [PubMed: 16809633]

Rai R, Chen Y, Lei M, & Chang S (2016). TRF2-RAP1 is required to protect telomeres from engaging in homologous recombination mediated deletions and fusions. Nature Communications 4(7) 10881.

Rangel-Moreno J, Hartson L, Navarro C, et al. (2006). Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. The Journal of Clinical Investigation 116, 3183–3194. [PubMed: 17143328]

Rappaport SM (2011). Implications of the exposome for exposure science. Journal of Exposure Science & Environmental Epidemiology 21, 5–9. [PubMed: 21081972]

Rappaport SM, & Smith MT (2010). Environment and disease risks. Science 330,460–461. [PubMed: 20966241]

Reddel RR (2003). Alternative lengthening of telomeres, telomerase, and cancer. Cancer Letters 194, 155–162. [PubMed: 12757973]

Rees D, & Murray J (2007). Silica, silicosis and tuberculosis. The International Journal of Tuberculosis and Lung Disease 11, 474–484. [PubMed: 17439668]

Reste J, Zvigule G, & Zvagule T (2014). Telomere length in Chernobyl accident recovery workers in the late period after the disaster. Journal of Radiation Research 55, 1089–1100. [PubMed: 25015931]

Roake CM, & Artandi SE (2016). Telomere-lengthening mechanism revealed. Nature 539, 35–36. [PubMed: 27760112]

Robichova S, Slamenova D, Gabelova A, et al. (2004). An investigation of the genotoxic effects of N-nitrosomorpholine in mammalian cells. Chemico-Biological Interactions 148, 163–171. [PubMed: 15276872]

Sampson MJ, Winterbone MS, Hughes JC, Dozio N, & Hughes DA (2006). Monocyte telomere shortening and oxidative DNA damage in type 2 diabetes. Diabetes Care 29(2), 283–289. [PubMed: 16443874]

Sandin S, & Rhodes D (2014). Telomerase structure. Current Opinion in Structural Biology25, 104–110.

Schafer MJ, White TA, Iijima K, et al. (2017). Cellular senescence mediates fibrotic pulmonary disease. Nature Communications 8, 14532.

Schober SE, Mirel LB, Graubard BI, Brody DJ, & Flegal KM (2006). Blood lead levels and death from all causes, cardiovascular disease, and cancer: Results from the NHANES III mortality study. Environmental Health Perspectives 114, 1538–1541. [PubMed: 17035139]

Seow WJ, Cawthon R, Purdue MP, et al. (2014). Telomere length in white blood cell DNA and lung cancer: A pooled analysis of three prospective cohorts. Cancer Research 74, 4090–4098. [PubMed: 24853549]

Serrano AL, & Andrés V (2004). Telomeres and cardiovascular disease: Does size matter? Circulation Research 94(5), 575–584. [PubMed: 15031270]

Sfeir A, & de Lange T (2012). Removal of shelterin reveals the telomere end-protection problem. Science 336, 593–597. [PubMed: 22556254]

Shammas MS (2011). Telomeres, lifestyle, cancer, and aging. Current Opinion in Clinical Nutrition and Metabolic Care 14(1), 28–34. [PubMed: 21102320]

Shay JW, & Bacchetti S (1997). A survey of telomerase activity in human cancer. European Journal of Cancer 33, 787–791. [PubMed: 9282118]

Shen M, Cawthon R, Rothman N, et al. (2011). A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. Lung Cancer 73, 133–137. [PubMed: 21507503]

Shoeb M, Joseph P, Kodali V, et al. (2017). Silica inhalation altered telomere length and gene expression of telomere regulatory proteins in lung tissue of rats. Scientific Reports 7(1) 17284. [PubMed: 29230030]

Shoeb M, Kodali V, Farris BY, et al. (2017). Oxidative stress, DNA methylation, and telomere length changes in peripheral blood mononuclear cells after pulmonary exposure to metal-rich welding nanoparticles. NanoImpact 5, 61–69. [PubMed: 30734006]

Shoeb M, Mustafa G, & Joseph J (2019). Initiation of pulmonary fibrosis after silica inhalation in rats is linked with dysfunctional shelterin complex and DNA damage response. Scientific Reports 9, 471. [PubMed: 30679488]

Shoeb M, Mustafa GM, Kodali VK, et al. (2020). A possible relationship between telomere length and markers of neurodegeneration in rat brain after welding fume inhalation exposure. Environmental Research 180, 108900. [PubMed: 31711660]

Sjogren B, Fossum T, Lindh T, & Weiner J (2002). Welding and ischemic heart disease. International Journal of Occupational and Environmental Health 8, 309–311. [PubMed: 12412847]

Smogorzewska A, Karlseder J, Holtgreve-Grez H, Jauch A, & de Lange T (2002). DNA ligase IV dependent NHEJ of deprotected mammalian telomeres in G1 and G2. Current Biology 12, 1635–1644. [PubMed: 12361565]

de Souza MR, et al. (2018). Shorter telomere length and DNA Hypermethylation in peripheral blood cells of coal workers. Mutation Research, Genetic Toxicology and Environmental Mutagenesis 836(Pt B) 36–41.

SPECIAL NIOSH HAZARD REVIEW (1993). DHHS (NIOSH) Publication Number 93–106. https://www.cdc.gov/niosh/docs/93-106/default.html.

Srinivas N, Rachakonda S, & Hielscher T (2019). Telomere length, arsenic exposure and risk of basal cell carcinoma of skin. Carcinogenesis 40(6), 715–723. [PubMed: 30874287]

Sriram K, Lin GX, Jefferson AM, et al. (2010). Mitochondrial dysfunction and loss of Parkinson's disease-linked proteins contribute to neurotoxicity of manganese-containing welding fumes. The FASEB Journal 24(12), 4989–5002. [PubMed: 20798247]

Stewart JA, Wang F, Chaiken MF, et al. (2012). Human CST promotes telomere duplex replication and general replication restart after fork stalling. The EMBO Journal 31, 3537–3549. [PubMed: 22863775]

Stout GJ, & Blasco MA (2013). Telomere length and telomerase activity impact the UV sensitivity syndrome xeroderma pigmentosum C. Cancer Research 73, 1844–1854. [PubMed: 23288511]

Stracker TH, & Petrini JH (2011). The MRE11 complex: Starting from the ends. Nature Reviews. Molecular Cell Biology 12, 90–103. [PubMed: 21252998]

Umbright C, Sellamuthu R, & Roberts JR (2017). Pulmonary toxicity and global gene expression changes in response to sub-chronic inhalation exposure to crystalline silica in rats. Journal of Toxicology and Environmental Health. Part A 80(23–24), 1349–1368. [PubMed: 29165057]

Uziel O, Singer JA, & Danicek V (2007). Telomere dynamics in arteries and mononuclear cells of diabetic patients: Effect of diabetes and of glycemic control. Experimental Gerontology 42(10), 971–978. [PubMed: 17709220]

Vallieres E, Pintos J, Lavoue J, et al. (2012). Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: Evidence from two case-control studies in Montreal. Cancer Medicine 1, 47–58. [PubMed: 23342253]

Van Ly D, Low RRJ, & Frölich S (2018). Telomere loop dynamics in chromosome end protection. Molecular Cell 71(4) 510–525.e6. [PubMed: 30033372]

Vlaanderen J, Taeger D, Wellman J, et al. (2013). Extended cancer mortality follow-up of a German rubber industry cohort. Journal of Occupational and Environmental Medicine 55(8), 966–972. [PubMed: 23887703]

de Vocht F, Sobala W, Wilczynska U, et al. (2009). Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. Cancer Epidemiology 33, 94–102. [PubMed: 19679054]

Vupputuri S, Parks CG, Nylander-French LA, et al. (2012). Occupational silica exposure and chronic kidney disease. Renal Failure 34, 40–46. [PubMed: 22032652]

Watson JD (1972). Origin of concatemeric T7 DNA. Nature: New Biology 239, 197–201. [PubMed: 4507727]

Weisburger JH, & Williams GM (1983). The distinct health risk analyses required for genotoxic carcinogens and promoting agents. Environmental Health Perspectives 50, 233–245. [PubMed: 6873017]

Wong JYY, De Vivo I, Lin X, & Christiani DC (2014). Cumulative PM2.5 exposure and telomere length in workers exposed to welding fumes. Journal of Toxicology and Environmental Health, Part A: Current Issues 77, 441–455.

Wu P, Takai H, & de Lange T (2012). Telomeric 3′ overhangs derive from resection byExo1 and Apollo and fill-in by POT1b-associated CST. Cell 150, 39–52. [PubMed: 22748632]

Wu Y, Liu Y, Ni N, et al. (2012). High lead exposure is associated with telomere length shortening in Chinese battery manufacturing plant workers. Occupational and Environmental Medicine 69, 557–563. [PubMed: 22539657]

Wynn TA, & Ramalingam TR (2012). Mechanisms of fibrosis: Therapeutic translation for fibrotic disease. Nature Medicine 18, 1028–1040.

Xu Y, Lindh CH, Jönssonet BAG, et al. (2018). Occupational Exposure to Asphalt Mixture During Road Paving Is Related to Increased Mitochondria DNA Copy Number: A Cross-Sectional Study. Environmental Health 17(1), 29. [PubMed: 29587765]

Zhang X, Lin S, Funk WE, & Hou L (2013). Environmental and occupational exposure to chemicals and telomere length in human studies. Occupational and Environmental Medicine 70, 743–749. [PubMed: 23775864]

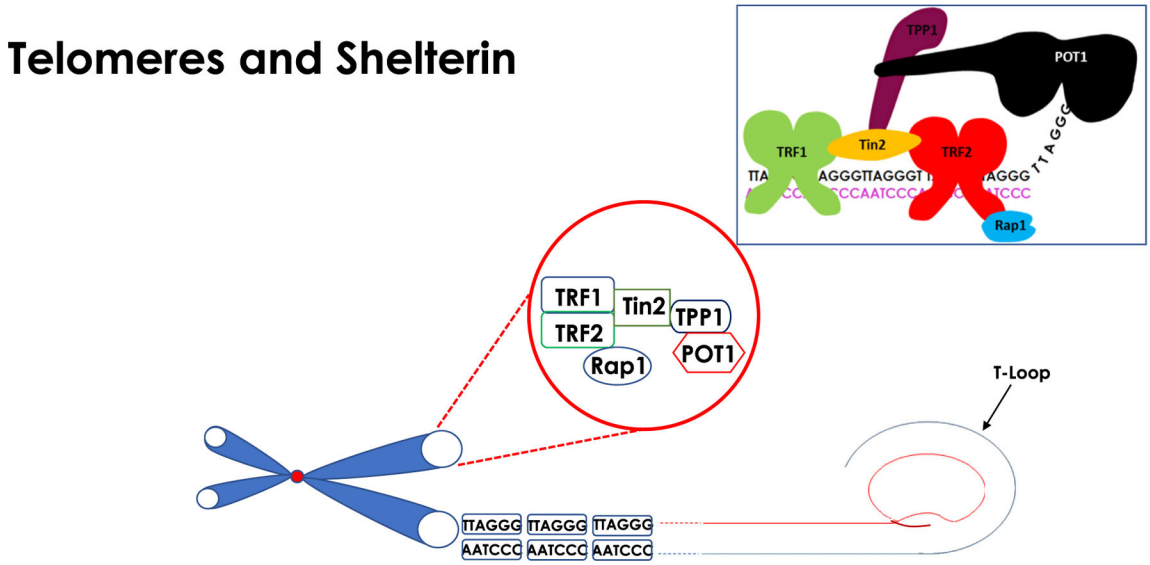

Fig. 1.

Schematic of the telomere in the t-loop configuration associated with shelterin complex which comprises POT1, TRF1, TRF2, TIN2, TPP1 and RAP1 (upper right). Telomeres are composed of the repetitive sequence (TTAGGG)n and are shielded by shelterin protein complex (upper right). TRF1 and TRF2 bind to the ds-telomere-DNA and POT1 interacts with ss-telomere-DNA. TPP1 is connected with POT1 resulting in bridge formation to TRF1 and TRF2 by associating with TIN2 (upper right).

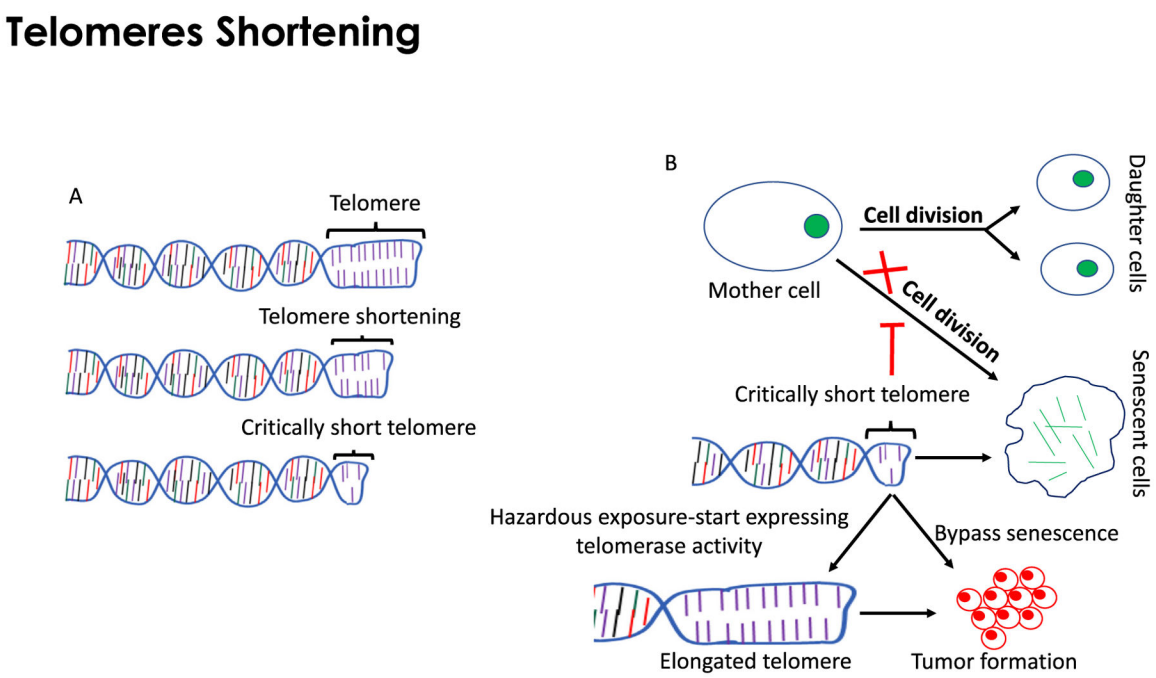

Fig. 2.

Schematic presentation of telomere shortening and cellular senescence. (A) Telomere repeats (TTAGGG)n are lost during each round of cell division resulting in telomere shortening and eventually critically short telomeres. (B) Cells without telomerase undergo the end replication problem resulting in critically short telomeres and initiate a program of cellular senescence. Sometimes the cells with critically short telomeres bypass the senescence signal and start expressing elevated telomerase activity, thereby extending the cell life span and amplified proliferation resulting in tumor cells.

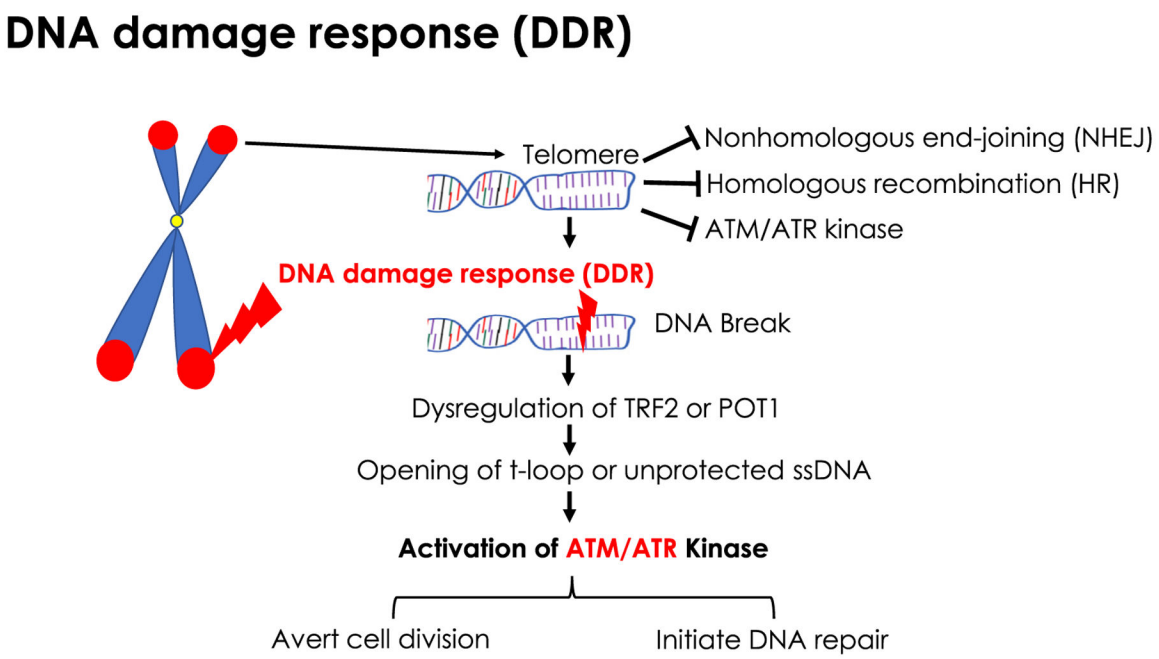

Fig. 3.

Telomere signaling pathway linking DNA damage response (DDR) and activation of ATM/ATR kinase, cycle arrest, and initiation of DNA damage. Telomeres repress NHEJ, HR, and ATM/ATR as indicated (⊤). Triggering of DDR may result in opening of t-loop and bare ssDNA through alteration of TRF2 or POT1 leading to induction of ATM/ATR kinases which then either prevent cell division or initiate DNA repair mechanisms.

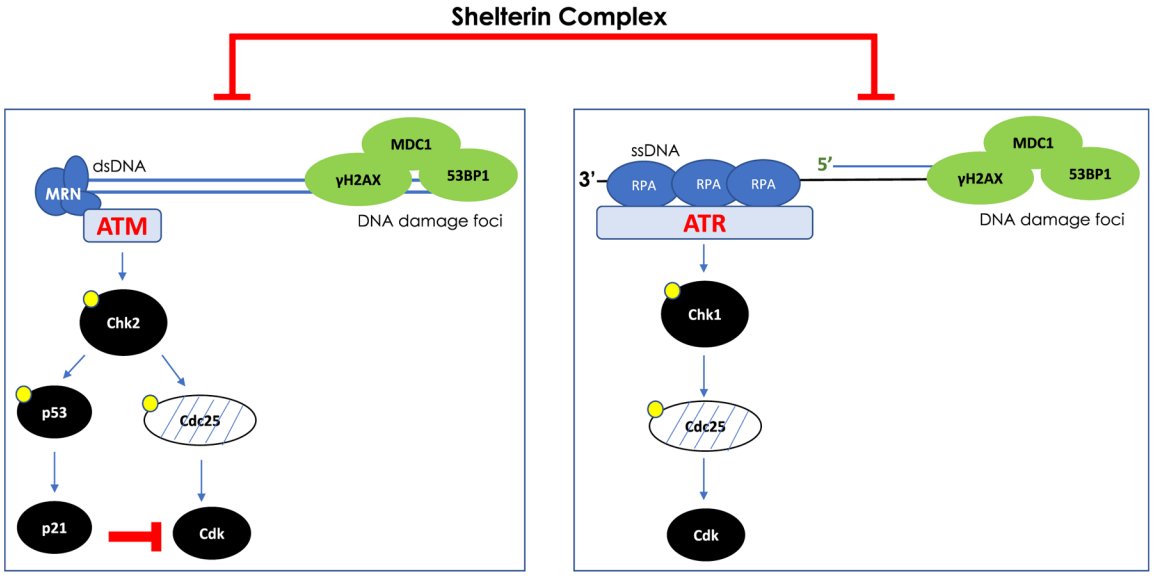

Fig. 4.

Activation of ATM and ATR kinase are inhibited by shelterin complex TRF2 and POT1. Shelterin component TRF2 prevents ATM signaling by preventing the loading of Mre11/ Rad50/ Nbs1 (MRN) complex at ds-telomere-DNA, whereas shelterin component POT1 prevents ATR signaling by preventing the loading of RPA at ss-telomere-DNA. Dysregulation of TRF2 or POT1 result in activation of ATM or ATR kinase at telomere, leading to accumulation of DNA damage foci (γH2AX, MDC1 and 53BP1) and cell cycle arrest.