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A glance at … telomeres, oxidative stress, antioxidants, and biological aging

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Telomeres, senescence, and biological aging

The "telomeric theory of biological aging" suggests that the ability of an individual cell to continue reproducing itself is limited by replication-induced shortening of chromosomal telomeres [1–5]. Human telomeres are strings of nucleotides located on the tips of chromosomes that repeat a "nonsense" sequence that does not code for any gene, TTAGGG, thousands of times [1]. Instead of providing genetic information, telomeres protect chromosomal integrity by extending chromosomes beyond their last genes. During DNA replication, the DNA polymerase-containing replication complex cannot fully replicate the 3′ end of linear duplex DNA during DNA replication (the "end-replication problem"). Any genetic information at that end of the molecule would be replicated in a truncated, potentially dysfunctional form [2]. Telomeres protect terminal genes from truncation by serving as expendable terminal nucleotide sequences that are sacrificed during every mitotic event [2]. The last telomeres on the 3′ end of a chromosome combine with a set of proteins (the shelterin complex) to form loop-like structures that prevent the "loose" ends of chromosomal DNA strings from being mistakenly identified by the DNA repair machinery as broken DNA strands that require repairing [3]. Because the chromosomes are not damaged, misguided repair attempts that could produce harmful mutations are prevented [1,3].

Because the terminal telomere/shelterin complex prevents DNA polymerase from accessing the DNA strand between replication cycles, it must be excised before DNA replication can occur, shortening the telomeric end of the chromosome by the number of lost telomere nucleotides [1]. Excised telomeric DNA is not replaced and the number of telomeric TTAGGG repeats on the end of each chromosome decreases with each round of DNA replication (telomere attrition) [1,3,4]. However, no genetic information is lost, and the shelterin complex reassociates with the remaining terminal telomeres, resuming its protective role [1–3].

A consequence of this process is that the average lengths of telomeres in most populations of human cells that are not terminally differentiated decline steadily with increasing chronologic age [6]. Progressive telomere attrition reflects the increasing numbers of previous replication cycles (replicative aging), limits the number of future cycles of DNA replication (and therefore the number of mitotic cycles and cell divisions) that remain available to the cell (the "Hayflick limit"), and acts as a molecular clock ("replicometer") tracking the reproductive history of a cell [4,5].

Although tissues with more rapid cellular turnover (such as intestinal epithelial cells) exhibit more rapid rates of telomere shortening [7], and telomere length will vary among individual chromosomes and cells [6], the average rates of telomere shortening in most tissues are highly correlated throughout adult life [6,8–11]. Because, on average, the telomeres of circulating leukocytes appear to decrease in length at a nearly constant rate throughout adult life [6], and because examining telomeres in freshly harvested leukocytes has become routine, the age-adjusted mean length of leukocyte telomeres in a sample of an individual's blood (mean leukocyte telomere length [LTL]) often is used as a biomarker of remaining biological life span in humans [6,8,11].

After a critical cell type–specific number of telomeric repeats have been lost ("telomeric crisis"), the telomere–shelterin complex destabilizes, sheds shelterin (telomere uncapping), and can no longer prevent the detection of a (false) DNA break and the initiation of a DNA damage response (DDR) [4,12]. The DDR begins with the detection of apparent DNA strand breaks and triggers a DNA replication-arresting cascade that prevents both potentially mutant DNA replication and the reproduction of a cell potentially containing mutant DNA [10,12]. Consistent with the hypothesis that there is an association between replicative aging and biological aging, the proportion of circulating human lymphocytes undergoing telomere attrition–associated DDR increases with increasing chronologic age [13].

Organismal longevity may reflect the integration of the replicative histories of all of the cell populations of the organism. For example, the numbers of cell divisions until permanent mitotic arrest and cellular senescence in freshly harvested

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human vascular smooth muscle cells (VSMCs) and endothelial cells were inversely correlated with donor age [14]. The available observational and experimental data also support the conclusion that cellular replicative capacity decreases, senescent cells accumulate, and functional senescence increases as individuals age [10]. For example, among a subset of the participants in the prospective Cardiovascular Health Study, those with the shortest age- and sex-adjusted LTL at the beginning of the study were 60% less likely to be living 5 years later (95% confidence interval, 22%–112%) [15].

Oxidative stress and replicative senescence

Biological and physiological aging are affected by the rate of whole-body free-radical production and oxidant–antioxidant imbalance contributes to human degenerative diseases of aging [16]. Reproductively senescent human cells produce increased amounts of reactive oxygen species (ROS) [17] that oxidatively damage DNA, including at telomeres [18].

The telomere strand of TTAGGG repeats is rich in guanine residues that are readily oxidized to 8-oxyguanosine (8-OHdG; 8-oxo-dG) [19]. The presence of 8-OHdG produces G→T transverse mutations within terminal telomeres that can accelerate telomere shortening by preventing the binding of protective shelterin proteins to the altered telomere and adjacent oxidatively modified telomeres form clusters that are less likely to be repaired [19,20]. In one study, mean telomere lengths in aortic endothelial cells, VSMCs, lymphocytes, and keratinocytes were inversely correlated with intracellular 8-OHdG content [21].

Experiments with freshly harvested human cells have demonstrated that oxidatively damaged DNA is a characteristic associated with accelerated telomere attrition and premature replicative senescence [22]. Additionally, shortened telomeres are more sensitive to oxidizing conditions, accelerating loss of replicative capacity and the onset of cellular senescence [23]. For example, among healthy premenopausal women, those with the greatest degree of chronic oxidative stress (reflected in the ratio of total isoprostanes to vitamin E within circulating leukocytes) had age-adjusted LTL that were shorter by an amount equivalent to an additional decade of biological aging [24]. Consistent with the hypothesis that oxidative stress accelerates telomere attrition, in a cross-sectional study of men aged 79 to 98 y, age-adjusted LTL was directly correlated with total circulating antioxidant capacity, suggesting that reducing systemic oxidative stress contributes to the preservation of telomere length [13].

Environmental sources of oxidative stress also induce premature cellular senescence. Pesticides such as dichlorodiphenyltrichloroethane stimulate lipid peroxidation, increase free-radical generation, accelerate the formation of 8-OHdG, and reduce mean telomere length [25]. Additionally, age-adjusted LTL was inversely correlated with the degree of exposure to vehicular emissions in a cross-sectional study in Milan, Italy [26], and in the prospective Veterans Affairs Normative Aging Study [27].

Telomere attrition and age-associated conditions

Cardiovascular disease

Accelerated telomere attrition may contribute to coronary heart disease [28]. When the data from a pair of 19-year prospective studies of 19,838 Danes (the Copenhagen City Heart Study; the Copenhagen General Population Study) were combined, it was calculated that for every 1000 base-pair decrease in age-adjusted average LTL, the risk for experiencing a myocardial infarction increased 10%, the risk for developing ischemic heart disease increased 6%, and the risk for suffering premature death increased 9% [29]. A study of patients referred for coronary angiography found a direct correlation between age-adjusted average peripheral blood mononuclear cell telomere length and years of survival postangiography [30].

Osteoarthritis

Senescent chondrocytes have been observed within osteoarthritic articular cartilage lesions [31]. In articular cartilage tissues harvested from both morphologically healthy and osteoarthritic human femoral heads, the number of short telomeres (consisting of <1500 base pairs) per unit surface area was directly correlated with the degree of apparent cartilage degeneration [32]. Men and women in the TwinsUK Adult Twin Registry with hand osteoarthritis had significantly shorter LTLs [33].

Glucoregulation

In the 5.5-y prospective observational Strong Heart Family Study of 2328 initially normoglycemic male and female Native Americans, the multivariate-adjusted hazard ratio for the development of type 2 diabetes was doubled for those individuals with the shortest age-adjusted LTL [34]. A meta-analysis of nine case–control studies concluded that the risk for developing type 2 diabetes is 12% greater when the age-adjusted LTL is less than the average length among adults without impaired glucose homeostasis [35]. However, it is not clear whether telomere shortening disrupts glucoregulation or loss of glucoregulation produces an increase in systemic oxidative stress that disrupts telomere length homeostasis [36].

Cognition

Among a group of men and women aged 33 to 79 y, performance on an intelligence test was correlated with age-adjusted LTL [37]. In other studies, men aged ≥65 y living in Hong Kong [38] and women 19 to 78 y old living in the United Kingdom [39] exhibited memory recall speed and accuracy that were correlated with age-adjusted LTL. Furthermore, among a group of men and women aged 64 to 75 y and exhibiting no signs of dementia, the degrees of subcortical cerebral atrophy (a correlate of cognitive decline) and white matter hyperintensities (a correlate of cerebral infarcts) were each inversely correlated with the age-adjusted LTL [40].

Diet, nutritional antioxidants, telomere attrition, and replicative senescence

Because exposure to ROS-induced oxidative stress accelerates telomere shortening, and telomere shortening is associated with accelerated biological aging and premature replicative senescence, reducing the ratio of oxidants to antioxidants should retard telomere attrition, decelerate cellular aging, and delay the onset of replicative senescence. There is evidence that dietary enhancement of systemic antioxidant capacity can beneficially influence cellular and biological aging. In retrospective observational studies, age-adjusted LTL was significantly shortened among those individuals with the smallest routine daily intakes of fruits [41–44] and was directly correlated with total daily fruit and vegetable intakes [42–45]. In the cross-sectional Sister