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Oxidative Telomere Attrition, Nutritional Antioxidants and Biological Aging

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Abstract

Telomeres are strings of DNA that are not themselves genes but that extend every chromosome beyond its last gene. Terminal telomeres are sacrificed during every mitotic event in human cells ("telomere attrition"), preserving the functional genome despite the "end replication problem." However, the "telomeric theory of biological aging" suggests that when an individual cell has reproduced itself a sufficient number of times (the "Hayflick limit"), some the its telomeres have become critically shortened ("telomeric crisis") and cannot completely "cap off" a chromosome, and any further attempts to replicate such a chromosome would produce damaged DNA and a dysfunctional cell ("cellular aging"). As cells enter telomeric crisis, they usually initiate intracellular signaling cascades that arrest DNA replication and mitotic activity, converting biologically active cells into inactive cells ("cellular senescence"). The progressive accumulation of senescent cells impairs the healthy functioning of tissues and produces "biological aging."

Oxidative stress damages telomeres and accelerates telomere attrition and biological aging. Premature biological aging is associated with degenerative diseases and diminished quality of life. Reducing the level of systemic oxidative stress can ease the oxidative drive toward cellular senescence and premature biological aging. Increased intakes of antioxidant-rich foods and specific antioxidant nutrients (such as fruits and vegetables, α-lipoic acid, astaxanthin, eicosapentaenoic acid, docosahexaenoic acid, *trans*-resveratrol, *N*-acetylcysteine, methylsulfonylmethane, lutein, vitamin C, vitamin D, vitamin E, and γ-tocotrienol) may decrease cellular and systemic oxidative stress and decelerate biological aging.

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Introduction

Telomeres, Senescence and Biological Aging

Human telomeres are strings of nucleotides located on the tips of chromosomes that repeat the "nonsense" sequence, TTAGGG, thousands of times.[1] Instead of providing genetic information, telomeres protect chromosomal integrity. 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 1) the "loose" ends of chromosomal DNA strings from being mistakenly identified by the DNA repair machinery as broken DNA strands that require repairing, and 2) subsequent well-intentioned but misguided repair attempts that could produce harmful mutations.[1-6]

When a cell is replicating its DNA prior to undergoing mitosis, 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 nformation at that end of the molecule would be replicated in a truncated, potentially dysfunctional form.[7] Telomeres protect terminal genes from truncation by serving as expendable terminal nucleotide sequences.[7] However, the terminal telomere/shelterin complex prevents the required relationship between DNA polymerase and the DNA strand, and must be excised before DNA replication can occur. Because the excised telomeric DNA is not replaced, the number of telomeric TTAGGG repeats on the end of each chromosome decreases with each round of DNA replication (telomere attrition).[1,2,4,6,8] However, no genetic information is lost, and the shelterin complex and remaining terminal telomeres reassociate, resuming their protective role.[1-7]

A consequence of this process is that the average lengths of telomeres in most populations of reproducing human cells (such as the fibroblasts that form a scar, or the circulating leukocytes that fight infections) decline steadily with increasing chronological age, reflecting increasing numbers of previous replication cycles.[9-17] This phenomenon has been observed in human peripheral blood mononuclear cells,[16,18-21] leukocytes,[9,11,13,19,22-54] lymphocytes,[12,55-58] bone marrow-derived hematopoietic stem cells,[59,60] oral cavity buccal cells,[16] skeletal muscle cells,[9,24] skin epidermal cells,[15,61] skin keratinocytes,[9,24] fibroblasts,[62] vascular endothelial cells,[19,63-65] adipocytes,[9,24] pituitary neurons,[66] and cells in the colon.[41,66,67] The rates of telomere shortening in different tissues appear to remain highly correlated and, on average, approximately linear throughout adult life.[9-17] However, tissues with more rapid cellular turnover (such as intestinal epithelial cells) exhibit more rapid rates of telomere shortening.[9,68,69]

At any given time, within a cell that is not terminally differentiated, the length of the remaining telomere string reflects the number of previous replication cycles the cell has experienced and 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").[4,7,8,62,70] Thus, telomeres act as a molecular clock ("replicometer") tracking the reproductive history of a cell.[8] The progressive telomere shortening that occurs during repeated cycles of cell division moves a cell toward its Hayflick limit (replicative aging).[8] After a critical cell type-specific number of telomeric repeats have been lost, 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^b).[8,71,72]

The DDR begins with the detection of DNA strand breaks and triggers a DNA replication-arresting cascade.[71-75] Activation of the $p16^{INK4A}$ tumor suppressor protein inhibits the D-type cyclin-dependent kinases, CDK4 and CDK6, that deactivate via phosphorylation the retinoblastoma tumor suppressor protein (Rb); Rb deactivation releases cells from arrest in the G1 phase of the cell cycle while $p16^{INK4A}$-initiated inhibition of Rb deactivation arrests DNA replication and mitosis.[68,73-79] Consequently, initiation of the $p16^{INK4A}$/

Rb cascade by the DDR prevents both potentially mutant DNA replication and the reproduction of a cell potentially containing mutant DNA.[68,73-79] Consistent with the hypothesis that there is an association between replicative aging and biological aging, the expression of $p16^{INK4a}$ (and, therefore, the likelihood of irreversible cessation of replication; replicative senescence) increases in human lymphocytes with increasing chronological age.[58]

The DDR also activates the tumor suppressor protein 53 (p53) – p21 (CDK-inhibitor 1A; CDKN1A) pathway to cell cycle arrest.[80] Activated p53 activates p21, triggering a cascade, sequentially involving the growth arrest and DNA-damage inducible protein 45 (GADD45), mitogen-activated protein kinase 14 (MAPK14), growth factor receptor-bound protein 2 (GRB2), transforming growth factor-β receptor 2 (TGFBR2), steroid receptor coactivator (Src), the disabled-2 (Dab2) intracellular adaptor protein, and transforming growth factor-β (TGF-β), that induces a positive feedback loop of mitochondrial dysfunction, increased oxidative DNA damage, and inability to perform replicative functions that drives the cell toward replicative senescence.[4,7,73,74,80-82]

Replicative senescence can be delayed. Replicating cells express telomerase, a constitutive ribonucleoprotein complex containing at least 6 and as many as 16 distinct proteins that is present at low activity in all cells that are not terminally differentiated.[22,83] The RNA component of telomerase (TERC) serves as a template for the "replacement" of telomeric DNA, while the catalytic subunit of telomerase (TERT) acts as a cellular reverse transcriptase, elongating replication-shortened telomeres by adding 5′-TTAGGG-3′ repeats.[7,22,84-86] Upregulation of telomerase activity is vital to the prevention, postponement or elimination of the continued shortening and inevitable replication-arresting uncapping of key telomeres (telomere crisis).[4,7,22,84-88] All healthy replicating human cells eventually experience a terminal telomere crisis, chromosomal instability, and apoptotic death.[87] The interplay between telomere attrition, telomerase upregulation, and the DDR, and the intensity and duration of their initiating stimuli, determines the eventual fate of the cell – resumed replication, replicative senescence, or apoptosis.

Telomerase activity and telomere lengthening are directly correlated with the expression of TERT.[88] Conversely, humans with mutated (inactive) TERT have proliferating cells with very short telomeres that, even during childhood, have average lengths similar to those of unmutated telomeres of adults years older;[22,89,90] these cells exhibit significantly reduced replicative capacities, with fewer cell divisions until replicative senescence.[91]

The activation of telomerase may be thought of as a mechanism to slow down the rate of progressive genomic instability that results from dysfunctional telomeres and the consequences of that instability.[92] For example, mice with epidermal stem cells lacking telomerase and exhibiting very short telomeres experienced delayed wound healing, stunted hair growth, epidermal thinning, dwarfism, stunting of individual internal organs, and reduced longevity,[93] which were reversed upon restoration of telomerase activity.[94] Consistent with these data, aging murine neuronal stem cells, in which the expression of telomerase is downregulated and telomeres are critically short and dysfunctional, produce daughter neurons that are fewer in number and unable to develop fully mature neurite arbors (differentiation failure).[95]

The limited life span of many human cell types that are not capable of replicating themselves results from their inability to express telomerase (because they are fully differentiated and not dividing) and maintain telomeres at sufficient lengths to suppress DDRs.[96] On the other hand, there is evidence that initially longer telomeres decrease in length most rapidly[18,97,98] and that a "telomere trimming" mechanism releases telomeric DNA from elongated telomeric chains despite the presence of active telomerase, counteracting "excessive" telomere lengthening and possibly setting upper limits on maximum telomere length and the

number of future replication cycles until senescence will be reached.[99-102]

Organismal longevity may reflect the integration of the replicative histories of all of the cell populations of the organism. Because the rates of telomere shortening in different tissues are highly correlated throughout adult life,[9,10,15,17] the mean lengths of telomeres in easily obtained peripheral blood mononuclear cells (PBMC) or circulating leukocytes (mean leukocyte telomere length; LTL) may serve as biomarkers of remaining biological lifespan in humans. 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 alive years later (95% confidence interval: 22%, 112%).[32] In contrast, mice that have been genetically engineered to overexpress telomerase experienced greater overall health and extended life span.[103]

The available observational and experimental data support the conclusion that cellular replicative capacity decreases, senescent cells accumulate, and functional senescence increases as humans grow older.[68] For example, when freshly-harvested human vascular smooth muscle cells and endothelial cells were studied, the numbers of cell divisions until permanent mitotic arrest and cellular senescence were inversely correlated with donor age.[104] In another study, compared to findings in men and women aged 20 to 39 years, a loss of replicative capacity was detected in the skin of men and women over 68 years old.[105] In contrast, pharmacological elimination of $p16^{INK4A}$-positive cells in mice delayed the appearance of typical "age-associated" degenerative changes, including reduction in DNA synthesis within skeletal muscle, loss of skeletal muscle diameter, decreased exercise ability, and increased numbers of apoptotic cells within the eyes.[106] Together, these findings suggest that cellular aging (biological aging) increases with chronological age and may be a consequence of cumulative telomere attrition.

Oxidative Stress and Replicative Senescence

The biological and physiologic processes associated with aging reflect the rate of whole-body free radical production,[107-111] and an imbalance in the body's oxidant and antioxidant status is an important etiologic factor for human degenerative diseases of aging.[107-112] Reproductively-senescent human cells in many tissues produce increased amounts of reactive oxygen species (ROS)[113] and contain oxidatively modified proteins that disrupt pathways involved in the inflammatory response, carbohydrate metabolism, nucleic acid metabolism, amino acid metabolism, protein synthesis, free radical scavenging, cell migration, and apoptotic cell death.[114-116] In addition, ROS contribute to the induction of replicative senescence through the creation of foci of oxidatively-modified DNA, including at telomeres.[117]

The telomere strand of TTAGGG repeats is particularly sensitive to oxidative stress because these strands are rich in guanine residues that are readily oxidatively modified to 8-oxyguanosine (8-OHdG; 8-oxo-dG).[118] 8-OHdG results in mostly G→T transverse mutations that can accelerate telomere shortening by reducing the protective binding of shelterin proteins to the altered telomere.[61,119] In addition, adjacent oxidatively-modified telomeres form clusters of oxidized DNA lesions that are less likely to be repaired successfully.[120,121] In a case-control study, telomere lengths in aortic endothelial cells, vascular smooth muscle cells, lymphocytes, and keratinocytes were inversely correlated with intracellular 8-OHdG content.[16] Cellular senescence also can result from telomere-independent oxidative chromosomal disruption, including DNA damage from radiation, oxidants, alkylating agents, and drugs that generate double-strand DNA breaks.[122]

Experiments with human dermal fibroblasts,[80,123-128] human adipocytes,[129] human vascular smooth muscle cells,[130-132] human arterial endothelial cells,[113] human umbilical vein endothelial cells,[132] and human retinal pigment epithelial cells[133] have provided evidence that oxidatively damaged DNA is a characteristic associated with accelerated telomere attrition and premature replicative senescence. In

response to continuous exposure to sublethal concentrations of hydrogen peroxide (H_2O_2), human cells increase superoxide production, experience elevated intracellular oxidative stress, and exhibit oxidative telomere shortening that accelerates with each subsequent replicative cycle. As shown in experiments with cultured human fibroblasts and endothelial cells exposed to H_2O_2, loss of telomerase activity results from export of the oxidatively-damaged reverse transcriptase subunit of telomerase out of the nucleus and into the cytosol through nuclear pores, preventing telomere length maintenance within the nucleus during replicative cycles.[113,134,135] In addition, shortened telomeres are more sensitive to oxidizing conditions.[130,136] These responses are accompanied by reductions in the numbers of cell divisions until replicative capacity is lost and cellular senescence ensues.

Exposing human vascular smooth muscle cells to superoxide anion-promoting angiotensin II[130,131] or exposing cultured human dermal fibroblasts to ultraviolet-A irradiation[128] resulted in increased generation of ROS and oxidative DNA damage that were accompanied by accelerated telomere attrition and premature replicative senescence. In cross-sectional[48] and case-control[80] studies, age-adjusted LTL were inversely correlated with the plasma concentration of total oxidizing compounds[48] and with an established biomarker of the level of systemic oxidative stress, the plasma concentration ratio of F_2-isoprostane lipid peroxidation products to the antioxidant, ascorbic acid.[80,137] Among a cohort of 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.[138] Consistent with the hypothesis that oxidative stress accelerates telomere attrition, in a cross-sectional study of men aged 79 to 98 years, age-adjusted LTL was directly correlated with total circulating antioxidant capacity, suggesting that reducing systemic oxidative stress contributes to the preservation of telomere length.[58]

Environmental sources of oxidative stress also induce premature senescence. Pesticides such as DDT (dichlorodiphenyltrichloroethane; 1,1,-trichloro-2,2-*bis*-chlorophenylethane) stimulate lipid peroxidation, increase free radical generation, accelerate the formation of 8-OHdG, and reduce the length of telomeres in buccal cells.[139-141] Humans exposed to large amounts of vehicular emissions exhibit increased systemic oxidative stress[142-144] that accelerates telomere attrition,[113,134] accelerating cellular biological aging[26] and organismal aging.[145] Vehicular emissions have been found to be highly tissue-oxidizing in several case-control studies[142-144] and age-adjusted LTL have been reported to be inversely correlated with the degree of exposure to vehicular emissions in a cross-sectional study in Milan, Italy,[146] and in the prospective Veterans Affairs Normative Aging Study.[147]

Cigarette smoke contains many oxidizing chemicals, including nitric oxide, nitrogen disulfide, nitric and nitrous oxide esters, and the superoxide-generating semiquinone radical.[148] Cigarette smoke produces systemic oxidative stress, depleting ascorbate, α-tocopherol, β-carotene, and glutathione reserves and stimulating the production of tissue-degenerating[114] and DNA strand-breaking[148] lipid peroxides, carbonylated proteins, and oxidized tyrosine residues.[149] Human fibroblasts express many proteins that are sensitive to oxidative stress[115] and upon reaching senescence, fibroblasts contain oxidatively modified proteins that disrupt pathways involved in the inflammatory response, carbohydrate metabolism, nucleic acid metabolism, amino acid metabolism, protein synthesis, amino acid metabolism, free radical scavenging, cell migration, and apoptotic cell death.[114] By increasing the oxidative modification of cellular proteins, cigarette smoking accelerates the biological aging of human tissues with probable negative impact on maximum chronological age.

Cigarette smoking also accelerates telomere attrition. In a cross-sectional study, age-adjusted LTL was inversely correlated with the number of cigarettes smoked lifetime, while DNA damage and lymphocyte

p16^{INK4a} expression were directly correlated with the number of cigarettes smoked lifetime and inversely correlated with age-adjusted LTL.[58] Cigarette smoking was associated with significantly accelerated rates of telomere attrition in the prospective Prevention of Renal and Vascular End-stage Disease study,[52] the cross-sectional Health, Aging and Body Composition[27] and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[21] studies, a case-control study conducted in Poland,[39] a cross-sectional study nested within the prospective Helsinki Businessmen Study[150] and case-control studies nested within the prospective all-male Health Professionals Follow-up Study and all-female Nurses' Health Study.[151] In addition, at the end of a 12-year prospective observational study, subjects who had quit smoking during the study exhibited significantly less continuing loss of telomere length than was experienced by continuing smokers.[47]

Cigarette-induced cellular senescence may be sufficiently severe to override the processes of replicative senescence. For example, in a study of arterial endothelial cells harvested from smoking and nonsmoking patients undergoing coronary artery bypass graft surgery, even though cells harvested from smokers exhibited increased production of 4-hydroxynonenal (HNE, a product of lipid peroxidation), impaired resistance to H_2O_2-induced oxidation of cellular contents, and increased expression of p53, these cells had experienced less telomere attrition prior to surgical harvest (possible reflecting the younger chronological age of the smoking patients at the time of life-saving surgery, which may have been preceded by fewer cell doublings).[152]

Telomere Attrition and Cancer

Excessive telomere attrition triggers a response that induces the expression of proteins that block the cell cycle and limits the replicative potential of cells.[4,7,8,71,73,74,80-82] In so doing, telomere attrition may protect against carcinogenesis by preventing the proliferation of cancerous cells. Observations of telomere shortening, genomic instability, and upregulated telomerase expression in many cancer tissues compared to adjacent normal tissue suggest that survival through a telomere crisis is a widespread crucial early event in malignant transformation.[153] Cells that escape crisis upregulate telomerase expression, reversing telomere loss,[62,154] or express telomerase variants that stabilize shortened telomeres.[55,155-157] Telomere stabilization at adequate but suboptimal levels can continue through an indefinite number of additional replication cycles, protecting genetically damaged DNA from normal cell senescence or apoptosis and allowing immortalized but damaged DNA to persist.[158] Alternatively, spontaneously immortalized cells that do not express telomerase (e.g., chromosomally stable microsatellite stable rectal cancer cells[159]) can maintain telomeres beyond "crisis" length through the telomerase -independent process of "alternative lengthening of telomeres" (ALT) during which new telomeric DNA is synthesized from a DNA template.[158-162]

Nonetheless, the telomeres in circulating leukocytes and in mixtures of peripheral blood mononuclear cells are shorter in humans with many types of cancers,[163] including gastrointestinal cancers, pancreatic cancer, bladder cancer, esophageal cancer, ovarian cancer, and lung cancer.[151,158,164-170] Premalignant lesions and tumors in which telomere lengths in cancer cells have been reported to be shortened even in the presence of active telomerase within the cancer cells include glioblastoma multiforme,[171] oral cancers,[172] and a variety of gastrointestinal tract cancers,[39,158] including esophageal squamous dysplasia and squamous cell carcinoma, Barrett's esophagus and esophageal adenocarcinoma, atrophic gastritis and gastric adenocarcinoma, pancreatic intraepithelial neoplasia and pancreatic adenocarcinoma and intraductal papillary mucinous neoplasm, and adenomatous polyp and colorectal adenocarcinoma. Telomere length in tumor cells appears to shorten early in the development of some cancers (e.g., low grade astrocytomas,[156] colorectal cancer,[173] oral cancers,[173] cervical cancer,[173] prostate cancer,[174] esophageal squamous cell carcinoma[158,173]) and the observation that telomere lengths in normal human esophageal[158] and mammary gland[175] epithelial cells adjacent to

cancerous lesions are shorter than in normal epithelial cells from individuals who do not have cancerous lesions suggests that telomere length stabilization after a period of accelerated telomere attrition is an early initiating event in these cancers.

The telomeres in circulating leukocytes and in mixtures of PBMC are shorter in the presence of many types of premalignant lesions and human cancers[163] and shortened age-adjusted LTL may serve as a biomarker of increased predisposition to carcinogenesis.[158,163,164] Although intralesional data are not available, age-adjusted LTL have been reported to be significantly shorter in individuals with oral premalignant lesions than in unaffected adults, and significantly shorter in patients with oral squamous cell carcinoma than in patients with premalignant lesions, and the risks of developing either lesions increased as age-adjusted LTL decreased.[176] Similar relationships have been reported for age-adjusted LTL and Barrett's esophagus and age-adjusted LTL and esophageal adenocarcinoma.[177] Consistent with the hypothesis that risk for cancer and age-adjusted LTL are inversely correlated, the combined results obtained from 47,102 Danish men and women in the 20-year prospective Copenhagen City Heart and Copenhagen General Population Studies indicated that survival after any cancer diagnosis was directly correlated with age-adjusted LTL.[45]

However, short LTL are not consistently associated with all cancers and accelerated telomere attrition may not be a general characteristic of precarcinogenesis. For example, in case-control studies nested within the all-male Physicians' Health Study,[178] the all-female Women's Health Study[179] and the male and female Norfolk cohort of the European Prospective Investigation into Cancer and nutrition study,[180] age-adjusted LTL were not correlated with risk for developing colorectal cancer. In a prospective study of prostate cancer risk, the risk of developing prostate cancer was not associated with short LTL;[40] in a New England case-control study, the risk for developing ovarian cancer was not correlated with age-adjusted LTL;[43] and in a case-control study nested within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the risk for developing glioma was not correlated with age-adjusted average buccal cell telomere length.[15] In addition, premature telomere shortening is not a feature of noncancerous colonocytes adjacent to colon carcinoma cells with shortened telomeres[66,181,182] or of noncancerous buccal mucosal cells adjacent to cancerous buccal mucosal cells with shortened telomeres.[174] Furthermore, short age-adjusted LTL have been associated with reduced risk for developing cutaneous melanoma[41] and short age-adjusted average telomere lengths in peripheral blood mononuclear cells have been associated with reduced risk for developing breast cancer.[20]

Telomere Attrition and Age-Associated Conditions

Replicative and cellular senescence are characteristic of human degenerative diseases.[48,183] For example, cardiovascular diseases that involve endothelial disruption or injury (including atherosclerosis,[63-65,69,184,185] coronary artery disease,[51,186] arterial trauma,[187] and abdominal aortic aneurysm[17]) are associated with accelerated telomere shortening in vascular endothelial cells, suggesting that the acceleration of telomere shortening may be a senescence-initiating response to endothelial injury. In addition, vascular smooth muscle cells harvested from human atherosclerotic plaques exhibit significantly shorter telomeres and significantly more oxidatively-damaged DNA than similar cells harvested from healthy tissue.[188]

Accelerated systemic telomere attrition is an attribute of most forms of cardiovascular disease. Significantly shorter age-adjusted LTL have been reported in individuals with coronary heart disease,[37] the odds of developing symptomatic peripheral arterial disease were inversely correlated with the age-adjusted LTL,[38,90] with a 15% increase in risk for every 10% decrease from the population mean in the age-adjusted LTL,[90] the maximum ultrasonically-measured thickness of the internal carotid artery wall (a biomarker for the extent of vascular disease[189]) was inversely correlated with the age-adjusted LTL,[26] and the odds of experiencing a stroke or of developing hypertension

were significantly increased among adults with age-adjusted LTL shorter than the population median.[34,51]

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 leukocyte telomere length, the risk for experiencing a myocardial infarction increased 10% (95% CI: 1%, 19%), the risk for developing ischemic heart disease increased 6% (95% CI: 0%. 11%), and the risk for suffering premature death increased 9% (95% CI: 5%, 13%).[190] Among 203 men in Salamanca, Spain, with symptomatic acute coronary syndrome and aged 50 to 75 years, the likelihood of survival was significantly lower for patients with age-adjusted LTL that were shorter than the median length for this cohort of men.[191] 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 post-angiography.[192]

Accelerated telomere attrition also may contribute to the etiology of osteoarthritis. Men and women in the TwinsUK Adult Twin Registry with hand osteoarthritis had significantly shorter leukocyte telomere lengths.[193] In addition, senescent chondrocytes have been observed within osteoarthritic articular cartilage lesions.[194] In articular cartilage tissues harvested from both morphologically healthy and osteoarthritic human femoral heads, the number of short telomeres (consisting of less than 1500 base pairs) per unit surface area was directly correlated with the degree of apparent cartilage degeneration.[195] Human articular chondrocytes are sensitive to oxidative stress and respond to H_2O_2 with increased production of ROS and increased cellular senescence, reflected in shortening of telomeres, reduced replicative capacity, and suppressed production and increased degradation of extracellular matrix macromolecules.[196]

Glucoregulation also is affected by telomere attrition. In the 5.5-year 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.[197] Consistent with these data, type 2 diabetes was associated with significantly shorter age-adjusted LTL in a cross-sectional study of Caucasian, South Asian, and Afro-Carribean men and women.[53] A meta-analysis of 9 case-control studies concluded that the risk for developing type 2 diabetes is 12% greater (95% CI: 0%, 25%) when the age-adjusted LTL is less than the average length among adults without impaired glucose homeostasis.[198] 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.[199]

Human lung function is correlated with age-adjusted LTL. The results of a meta-analysis of the results of previously published case-control and cross-sectional studies indicated that the odds of developing chronic obstructive pulmonary disease (COPD) or asthma were inversely correlated with the age-adjusted LTL.[200] In addition, both forced vital capacity and forced expiratory volume in one second were directly correlated with the age-adjusted LTL.[200]

Cognitive abilities may be reflected in age-adjusted LTL. For example, among a group of men and women aged 33 to 79 years, performance on an intelligence test was correlated with age-adjusted LTL.[35] In other studies, men 65 years old and older living in Hong Kong[201] and women 19 to 78 years old living in the United Kingdom[202] 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 years and exhibiting no signs of dementia, the degrees of subcortical cerebral atrophy (a correlate of cognitive decline) and of white matter hyperintensities (a correlate of cerebral infarcts) were each inversely correlated with the age-adjusted LTL.[203]

Diet, Nutritional Antioxidants, Telomere Attrition, and Replicative Senescence

Because exposure to ROS-induced oxidative stress accelerates telomere shortening,[123,124] and telomere shortening is associated with accelerated biological aging and premature replicative senescence,[123,124,204-206] reducing the generation of ROS and increasing antioxidant availability should provide potent mechanisms to retard telomere attrition, decelerate cellular aging, and delay the onset of replicative senescence.[61,206,207] For example, in a short nonblinded, randomized trial, the effects of 3 diets on telomere attrition were examined in men and women over 65 years old.[208] Serum drawn from the subjects while consuming the diet with the lowest content of saturated fatty acids was associated with the slowest rate of telomere attrition when the serum was added to the culture medium of human umbilical vein endothelial cells. This finding is consistent with results from several cross-sectional studies in which the age-adjusted LTL was inversely correlated with habitual daily intake of saturated fatty acids,[48,49,209,210] and a small 5-year prospective intervention in which a reduction in saturated fatty acid intake was associated with arrest of age-associated telomere shortening.[211]

There also 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 subjects with the smallest routine daily intakes of fruits[39,48,49,209] and was directly correlated with total daily fruit and vegetable intakes.[21,48,49,209] In the cross-sectional Sister Study, the mean multivariate-adjusted leukocyte telomere length was directly correlated with the daily consumption of a multivitamin supplement and, individually, with the daily intakes from foods of vitamin A, vitamin C, vitamin E, and folate.[212] In agreement with the results of the Sister Study,[212] a growing body of scientific evidence also supports the hypothesis that the addition of supplemental nutrients can contribute to a reduction in the rates of cellular and biological aging.

α-Lipoic Acid

α-Lipoic acid (5-(1,2-dithiolan-3-yl)-pentanoic acid) is a naturally-occuring component of human mitochondria that is able to penetrate both cell membranes and aqueous compartments, allowing it to act as a multi-purpose nonenzymatic antioxidant that protects mitochondria and surrounding cellular elements from oxidation by the free radicals produced by mitochondria during oxidative metabolism.[213-225] The sulfhydryl groups on the α-lipoic acid molecule provide strong antioxidant potency, directly exchanging free protons for free radical electrons in lipophillic environments (e.g., biological membranes) and exchanging free protons with hydroxyl ions and water during the deactivating reduction of free radical electrons in aqueous environments (e.g., biological fluids).[214]

In addition to reducing ROS, α-lipoic acid can recycle (reduce) other nonenzymatic antioxidants after they have become oxidized, prompting the descriptor, "antioxidant of antioxidants."[226-228] α-Lipoic acid also directly stimulates increased activities of a set of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase, and heme oxygenase-1 (HO-1).[216-220,223-229]

α-Lipoic acid can delay the onset of cellular senescence by downregulating the phosphorylation of Rb in cells with oxidatively damaged DNA, arresting cell cycle progression and redirecting the cells toward apoptotic death.[230] In addition, the initiation of oxidative damage to DNA can be prevented by α-lipoic acid, which has been shown to inhibit the formation of 8 -OHdG by the α,β-unsaturated aldehydes created during the free radical-induced oxidation of the membrane-associated ω-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA).[231]

Astaxanthin

Astaxanthin is a red carotenoid pigment found in salmon, crabs, and shrimp.[232,233] Following the consumption of astaxanthin by adults, peak plasma

astaxanthin concentrations of 10^{-8} *M* to 10^{-6} *M* have been observed; these peak concentrations were proportional to the amount of astaxanthin that was ingested.[234-238] Absorbed astaxanthin is taken up by most tissues of the body, including the kidneys, heart, liver, skin, skeletal muscle, eyes, lungs, brain, brain stem, and erythrocytes.[239-245]

The structure of astaxanthin confers extremely potent antioxidant powers. Its conjugated polyene structure allows astaxanthin to intercalate within the lipid bilayers of biological membranes[246] while its terminal hydroxylated ring structures remain exposed on the inner and outer surfaces of the membranes,[246,247] further increasing the number of free radical electrons that can be quenched by each molecule of astaxanthin[247] and preventing oxidative degradation of membrane structural integrity.[248-250] The spontaneous reactions of astaxanthin with oxidizing ROS[240,246,251-269] allow astaxanthin to exhibit free radical quenching potency that is double that of β-carotene,[246,255,270,271] 2 to 5 times that of DHA or eicosapentaenoic acid (EPA),[272] about 100-fold greater than that of α-tocopherol,[255-257] and approximately 6000 times the potency of ascorbic acid.[257] Astaxanthin also inhibits ROS formation by inhibiting spontaneous lipid peroxidation,[248-250,259,273-275] peroxyl radical-induced lipid peroxidation,[259,276] iron-induced oxidation of membrane phospholipids,[277-280] and the oxidation of low -density lipoprotein (LDL) particles.[281,282] Furthermore, exposure to astaxanthin increased the activities of the antioxidant enzymes, SOD, catalase, glutathione peroxidase, and glutathione reductase, and the intracellular concentration of the intracellular antioxidant, reduced glutathione, in human umbilical vein endothelial cells,[280,283] human neuroblastoma cells,[275] and murine retinal ganglion cells[266]

Absorbed astaxanthin is an active antioxidant in humans. Adolescent male soccer players exhibited significantly increased serum antioxidant capacity after 90 days of daily dietary supplementation with 4 mg of astaxanthin.[282] After supplementing their diets for 2 weeks with 6 mg of astaxanthin daily, men and women experienced a significant increase in the superoxide anion scavenging activity in the visual aqueous humor.[284] Supplementation with 20 mg of astaxanthin for 3 weeks[238] or 12 weeks[285] produced significant reductions in the plasma concentrations of the lipid peroxidation products, malondialdehyde (MDA) and F_2-isoprostane, reflecting reductions in whole-body cellular lipid peroxidation,[286,287] and significant increases in measured total circulating antoxidant capacity in 2 groups of overweight and obese men and women. Similarly, after 8 weeks of consuming 2 mg of astaxanthin daily, a group of healthy postmenopausal women exhibited a significantly greater increase in total plasma antioxidant status than was elicited by placebo, as well as a significantly greater reduction in the plasma concentration of thiobarbituric acid reactive substances (TBARS; mixed reaction products of nonenzymatic oxidative lipid peroxidation).[283,288] Another group of healthy postmenopausal women exhibited a significant increase in total circulating antioxidant activity after consuming 12 mg of astaxanthin daily for 8 weeks.[289]

Together these data indicate that astaxanthin reduces the level of oxidative stress throughout the body. Consistent with the hypothesis that oxidative stress increases the oxidative modification of DNA, shortens telomeres and promotes cellular senescence, while a reduction in systemic oxidative stress attenuates or reverses these responses, geriatric dogs fed 20 mg of astaxanthin daily for 16 weeks[290] and healthy young women who consumed 2 mg of astaxanthin daily for 8 weeks[291] experienced significant decreases in whole-body DNA oxidation.

ω-3 Fatty Acids

EPA (20:5ω3) and DHA (22:6ω3) are very long-chain polyunsaturated fatty acids that are dietary essentials because α-linolenic acid (18:3ω3), the immediate precursor of EPA, cannot be synthesized *de novo* in humans and must be consumed in the diet.[292-294] However, although it is the only known function of α -linolenic acid,[295-297] the conversion of α-linolenic acid to EPA is inefficient[298-302] and may not be adequate to fulfill physiological requirements for EPA and DHA.[303] A

small, biologically insignificant amount of DHA can be produced in humans by sequential elongation and desaturation of EPA.[292-294]

EPA and DHA contribute to telomere maintenance. In a 5-year prospective study of ambulatory outpatients with stable coronary artery disease, the multivariate-adjusted rate of leukocyte telomere shortening was inversely correlated with the combined whole blood concentrations of EPA and DHA.[304] In a double-blind, randomized placebo-controlled trial, daily supplementation with 180 mg of EPA plus 120 mg of DHA for 3 months reduced serum 8-OHdG concentrations and increased total circulating antioxidant capacity in cigarette smokers.[305] In another double-blind, randomized placebo-controlled trial, during which subjects consumed 2085 mg of supplemental EPA plus 348 mg of DHA daily for 4 months, lymphocyte telomere length was directly correlated with the increase in the combined plasma concentrations of EPA and DHA.[306] DHA may be the telomerically-relevant nutrient; among men and women over 65 years old, increased erythrocyte DHA content accompanying 6 months of increased DHA intake was inversely correlated with the rate of telomere shortening in whole blood.[307]

trans-Resveratrol

trans-Resveratrol (*trans*-3,4′,5-trihydroxystilbene) is a polyphenol produced by many plants, including raspberries, blueberries, grapeskins, peanuts, and certain pine trees.[207,308-310] Adding *trans*-resveratrol to the diet of laboratory animals or to the growth medium of cell cultures has been shown to support a number of physiologic systems,[311] including fatty acid mobilization from adipose stores,[312] energy metabolism in skeletal muscle[313-315] and articular cartilage,[316] reduction of oxidative damage and inflammation in metabolically active tissues,[313,316-325] and mitochondrial biogenesis with accelerated ATP regeneration and increased aerobic capacity, exercise tolerance, and endurance.[326,327] Rats fed *trans*-resveratrol at a rate of 20 mg to 50 mg per kg body weight (100 kg adult human equivalent daily intake: 30 to 80 mg[328]) increased the survival of hypoxia-challenged cardiac muscle,[329,330] attenuated cigarette smoke-induced and cardiovascular disease-producing loss of compliance by the carotid arteries,[331,332] prevented experimentally-induced autoimmune myocarditis,[333] stimulated the growth of new capillaries within the myocardium,[334] and attenuated the expression of biomarkers of aging in the heart.[335]

Other components of the cardiovascular system also benefit from *trans*-resveratrol consumption. Arterial endothelial cells harvested from rats exhibit attenuation of cigarette smoke-induced generation of ROS and secretion of the pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), in the presence of 10^{-4} *M* *trans*-resveratrol.[336] At a lower concentration (10^{-5} *M*), *trans*-resveratrol has attenuated oxidative DNA fragmentation and cellular death induced by TNF-α, H_2O_2, and oxidized LDL in rat arterial endothelial cells via increased expression of glutathione peroxidase, catalase, and heme oxygenase-1 (HO-1).[337]

Evidence from cultured human lung epithelial cells,[338] vascular endothelial cells[339] and human platelets[308,340-343] indicates that *trans*-resveratrol (10^{-5} *M*) stimulates glutathione synthesis and reduces the generation of ROS. Exposure of human arterial endothelial cells to *trans*-resveratrol (10^{-7} *M*) attenuates H_2O_2-induced endothelial cell adhesion to monocytes.[344] *trans*-Resveratrol (10^{-8} *M*) also inhibits superoxide production by human neutrophils[345] and vascular endothelial cells,[346] preventing ROS production by vascular smooth muscle cells.[347] *trans*-Resveratrol crosses the blood-brain barrier[348] and physiologic and near-physiologic concentrations of *trans*-resveratrol (10^{-7} *M* to 10^{-5} *M*) inhibit the neuronal production of ROS.[349-352]

These properties of *trans*-resveratrol combine to retard the rate of cellular senescence. Human peritoneal mesothelial cells exposed to *trans*-resveratrol (0.5 x 10^{-6}

M) experienced increased recruitment into cell cycle progression and replication, reduced telomere attrition, increased SOD activity, decreased oxidative damage to DNA with less formation of 8-OHdG, upregulation of DNA repair enzymes, and an increased number of cell divisions before becoming senescent.[353]

N-acetylcysteine

N-acetylcysteine is an acetylated variant and precursor of the amino acid, L-cysteine, serves as a precursor to glutathione (an endogenous reducer of lipid peroxides[283]), and is associated with free radical scavenging activity that may be related to its sulfhydryl groups.[354] Human trabecular meshwork cells grown in culture with a high concentration of oxidizing glycated albumin produced increased amounts of superoxide and total ROS and exhibited evidence of accelerated telomere attrition; these effects were attenuated when *N*-acetylcysteine was added to the culture medium.[355] The addition of *N*-acetylcysteine to cultures of human lymphocytes exposed to irradiation[356] and human astrocytoma cells infected with the human immunodeficiency virus[357] has attenuated increases in ROS production and decreases in the ratio of reduced to oxidized glutathione while maintaining longer telomere lengths. In addition, human arterial endothelial cells and human pluripotent stem cells respond to *N*-acetylcysteine with reduced production of ROS, less oxidative modification of DNA, a decrease in the number of genomic aberrations, increased telomerase activity, prevention of cell doubling-associated telomere attrition, delayed upregulation of the DDR pathway, and increased replicative capacity.[113,354,358,359] These responses are consistent with the conclusion that *N*-acetylcysteine delays cellular aging.

Methylsulfonylmethane

Methylsulfonylmethane (MSM) is an organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains, and animals.[360] The ingestion of MSM stimulates glutathione activity and reduces the lipid peroxidation caused by exercise. Sport horses given supplemental MSM during a season of competition exhibited significant increases in the plasma concentration of reduced glutathione and in the plasma activities of glutathione peroxidase, glutathione reductase, and glutathione transferase, and a significant decrease in the plasma concentration of total lipid peroxides.[361] Consistent with that report, healthy men participating in a randomized double-blind, placebo-controlled trial experienced significantly greater plasma concentrations of reduced glutathione and significantly lower plasma concentrations of lipid peroxidation products and protein carbonyls at the end of a 14 km run following 10 days of dietary supplementation with 50 mg of MSM per kg bodyweight.[362]

Vitamin C

Vitamin C is an essential nutrient that must be supplied through the diet because humans lack the enzyme, gulonolactone oxidase, and therefore cannot synthesize vitamin C *de novo*.[363] Ascorbate, the dominant form of vitamin C in humans, contains 2 enolic hydrogen atoms that provide electrons that are available for nonenzymatic transfer to ROS. The availability of two reducing equivalents per molecule of ascorbate provides the basis for the antioxidant properties of vitamin C, which readily scavenges ROS.[364] Oxidized ascorbate can be reduced back to ascorbate by transfer of its free radical electron to another receptor molecule or can be further oxidized to dehydroascorbate. In turn, dehydroascorbate can be recycled to ascorbate or can be converted into the excretory end product, 2,3-diketogulonate.[364]

In the cross-sectional Austrian Stroke Prevention Study, age-adjusted LTL was directly correlated with the plasma ascorbate concentration in elderly men and women.[365] Articular chondrocytes harvested from patients with osteoarthritis responded to ascorbic acid with increased production of extracellular matrix macromolecules, decreased degradation of extracellular matrix macromolecules, decreased production of ROS,

and improved maintenance of replicative capacity and telomere length.[196] These reports are consistent with a positive association between vitamin C intake, systemic antioxidant status, and telomere preservation.

Vitamin D

Vitamin D status, reflected in the serum concentration of 25-hydroxycholecalciferol (25-OHD_3),[366,367] itself a reflection of vitamin D intake,[368,369] affects human telomere attrition and cellular aging. For example, in a cross-sectional study of women aged 18 to 79 years in the UK, age-adjusted LTL was directly correlated with the serum 25-OHD_3 concentration and, compared to concentrations greater than 50 ng/mL, concentrations less than 25 ng/mL were associated with excessive telomere shortening equivalent to 5 additional years of telomere (and cellular) aging.[370] In another cross-sectional study, among vitamin D-deficient men and women, age-adjusted telomere attrition in PBMC was directly correlated with the degree of vitamin D deficiency.[371] In contrast, in a double-blind, randomized, placebo-controlled trial, 4 months of dietary supplementation with 60,000 IU of vitamin D once monthly increased the serum 25-OHD_3 concentration and was associated with significantly less telomere attrition in PBMC.[372]

Vitamin E

Vitamin E is a chain-breaking lipophillic antioxidant that reduces the lipid peroxyl radical produced during lipid peroxidation, interrupting self-sustaining sponaneous lipid peroxidation in a chain termination event.[283] By arresting lipid peroxidation cascades, vitamin E also slows human telomere attrition and cellular aging. Freshly harvested human skin fibroblasts grown in *ex vivo* culture exhibited increased resistance to H_2O_2-induced oxidative modification of DNA and acceleration of telomere attrition in the presence of 10^{-5} *M* α-tocopherol,[373] a physiologic concentration found in the plasma of adults who do not consume supplemental vitamin E.[374]

γ-Tocotrienol

The tocotrienols (α-,β-,γ-,δ-) are a group of naturally occurring, bioavailable, fat-soluble derivatives of vitamin E that exhibit antioxidant potency similar to or greater than that of α-tocopherol.[375] In a series of experiments in which skin fibroblasts were freshly harvested from young human foreskins and grown in cell culture until they reached senescence, γ-tocotrienol alone,[376,377] or as a component of a mixture of tocotrienols obtained from Malaysian palm oil,[378,379] increased the expression of antioxidant enzymes and of proteins required for cell proliferation; decreased ROS production, oxidative damage to DNA, and senescence-associated telomere shortening; and increased the number of cells that were released from cell cycle arrest. When similarly-obtained cells were cultured with H_2O_2 and γ-tocotrienol, telomere shortening and cell cycle arrest associated with increased intracellular oxidative stress were attenuated.[380,381] Coincubation with γ-tocotrienol also attenuated H_2O_2-induced cell cycle arrest in cultured young human myoblasts.[382] These data demonstrate that γ-tocotrienol retards telomere attrition and cell aging.

Lutein

The xanthophyllic carotenoid phytonutrient, lutein, accumulates in the macula lutea of the human retina.[383] In addition to causing the yellow color of that part of the eye, lutein protects the retina from the oxidizing effects of some of the ultraviolet light entering the eye.[383] In healthy women, compared to placebo, dietary supplementation with lutein (10 mg daily) for 12 weeks reduced by half the degree of epidermal lipid peroxidation while the resistance to ultraviolet light-induced erythema was increased 4- to 5-fold.[384] The antioxidant properties of lutein were evident in the cross-sectional Austrian Stroke Prevention Study, in which age-adjusted LTL was directly correlated with the serum lutein concentration in elderly men and women.[365] These results demonstrate that dietary lutein increases systemic antioxidant capacity and resistance to ultraviolet light-induced oxidative damage and contributes to telomere preservation.

Superoxide dismutase

SOD is an endogenous enzyme that reduces the superoxide anion to produce H_2O_2 (which is then reduced to H_2O and O_2 by catalase).[283,385] While the superoxide anion stimulates the oxidative drive toward cellular senescence,[130] its detoxification can promote delay of cellular senescence. For example, exposing human fibroblasts to exogenous SOD significantly reduced both the production of lipid peroxides and the rate of subsequent telomere shortening.[386] There also is a report that cells that are approaching senescence can be "cleared" by SOD-initiated conversion to the apoptotic pathway.[387]

Conclusions

Cellular oxidative stress accelerates telomere attrition and promotes cellular aging. Oxidatively damaged DNA predisposes individual cells to become senescent. The accumulation of senescent cells progressively impairs physiological functioning, is associated with degenerative diseases, and characterizes biological aging. Premature biological aging impairs health and diminishes the quality of life. Increasing the intakes of antioxidant-rich fruits and vegetables and supplementing the diet with α-lipoic acid, astaxanthin, EPA, DHA, *trans*-resveratrol, *N*-acetylcysteine, methylsulfonylmethane, lutein, vitamin C, vitamin D, vitamin E, and γ-tocotrienol may decrease cellular oxidative stress and decelerate biological aging.

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Conflict of Interest

This project was funded by Youngevity International, Inc., Chula Vista, CA, a manufactiurer of dietary supplements, and with whom Dr. Glade maintains a consultancy.

Abbreviations:

8-OHdG, 8-oxyguanosine;

8-oxo-dG, 8-oxyguanosine;

$25\text{-}OHD_3$, 25-hydroxycholecalciferol;

ALT, alternative lengthening of telomeres;

CDK4, cyclin-dependent kinase-4;

CDK6, cyclin-dependent kinase-6;

CDKN1A, cyclin-dependent kinase inhibitor 1A;

CI, confidence interval;

COPD, chronic obstructive pulmonary disease;

Dab2, diasabled adaptor protein 2;

DDR, DNA damage response;

DDT, dichlorodiphenyltrichloroethane; 1,1,-trichloro-2,2-*bis*-chlorophenylethane;

DHA, docosahexaenoic acid;

EPA, eicosapentaenoic acid;

GADD45, growth arrest and DNA-damage inducible protein 45;

GRB2, growth factor receptor-bound protein 2;

H_2O_2, hydrogen peroxide;

HNE, 4-hydroxynonenal;

HO-1, heme oxygenase-1;

LDL, low-density lipoprotein;

LTL, mean leukocyte telomere length;

MAPK14, mitogen-activated protein kinase 14;

MDA, malondialdehyde;

MSM, methylsulfonylmethane;

p21, cyclin-dependent kinase inhibitor 1A;

p53, tumor suppressor protein 53;

PBMC, peripheral blood mononuclear cells;

Rb, retinoblastoma tumor suppressor protein;

ROS, reactive oxygen species;

Src, steroid receptor coactivator;

SOD, superoxide dismutase;

TBARS, thiobarbituric acid reactive substances;

TERC, RNA component of telomerase;

TERT, catalytic subunit of telomerase;

TGF-β, transforming growth factor-β;

TGFBR2, transforming growth factor-β receptor 2;

TNF-α, tumor necrosis factor-α

Note: *Prior to undertaking a program of dietary supplementation, individuals should consult with a professional nutritionist or other healthcare professional trained in nutritional therapeutics.*

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