Report and Opinion

Websites:
http://www.sciencepub.net
http://www.sciencepub.net/report

Emails:
editor@sciencepub.net
reportopinion@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Telomere

Mark Herbert

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: The telomere is a region of repetitive nucleotide sequences associated with specialized proteins at the ends of linear chromosomes. Telomeres are a widespread genetic feature most commonly found in eukaryotes, which protect the terminal regions of chromosomal DNA from progressive degradation and ensure the integrity of linear chromosomes by preventing DNA repair systems from mistaking the very ends of the DNA strand for a double strand break.

[Mark Herbert. **Telomere** .*Rep Opinion* 2021;13(8):8-21]. ISSN 1553-9873 (print);ISSN 2375-7205 (online). http://www.sciencepub.net/report. 3.doi:10.7537/marsroj130821.03.

Keywords: telomere; chromosomes; DNA; nucleotide; protein; senescence; apoptosis

A telomere is a region of repetitive nucleotide sequences associated with specialized proteins at the ends of linear chromosomes. Although there are different architectures, telomeres, in a broad sense, are a widespread genetic feature most commonly found in eukaryotes. In most, if not all species possessing them, they protect the terminal regions of chromosomal DNA from progressive degradation and ensure the integrity of linear chromosomes by preventing DNA repair systems from mistaking the very ends of the DNA strand for a double strand break.

Discovery

In the early 1970s, Russian theorist Alexei Olovnikov first recognized that chromosomes could not completely replicate their ends, as an end replication problem. Cobsidering the Leonard Hayflick's theory of limited somatic cell division, Olovnikov suggested that DNA sequences are lost every time a cell replicates until the loss reaches a critical level, at which point cell division ends.[1]

In 1975–1977, Elizabeth Blackburn, working as a postdoctoral fellow at Yale University of USA with Dr. Joseph G. Gall, discovered the unusual nature of telomeres, with their simple repeated DNA sequences composing chromosome ends.[2] Blackburn, Carol Greider, and Jack Szostak were awarded the 2009 Nobel Prize in Physiology or Medicine for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.[3]

In 1983 Barbara McClintock received the Nobel Prize in Physiology or Medicine for observing that the chromosomes lacking end parts became sticky and hypothesized the existence of a special structure at the chromosome tip that would maintain chromosome stability.[4]

Structure and function

During DNA-replication, DNA synthesis can only attach new nucleotides to the 3'-end (synthesis progresses 5'-3') and it requires a primer to initiate the replication. On the leading strand 5'-3', DNA-polymerase continuously replicates from the point of initiation all the way to the strand's end with the primer then being excised and substituted by DNA. The lagging strand, however, is oriented 3'-5' with respect to the replication fork so continuous replication by DNA-polymerase is impossible, which necessitates discontinuous replication involving the repeated synthesis of primers further 5' of the site of initiation. The last primer to be involved in lagging-strand replication sits near the 3'-end of the template (corresponding to the potential 5'-end of the lagging-strand). Originally it was believed that the last primer would sit at the very end of the template, thus, once removed, the DNA-polymerase that substitutes primers with DNA (DNA-Pol δ in eukaryotes) would be unable to synthesize the "replacement DNA" from the 5'-end of the lagging strand so that the template nucleotides previously paired to the last primer would not be replicated.[5] It has since been questioned whether the last lagging strand primer is placed exactly at the 3'-end of the template and it was demonstrated that it is rather synthesized at a distance of about 70-100 nucleotides which is consistent with the finding that DNA in cultured human cell is shortened by 50-100 base pairs per cell division.[6]

If coding sequences are degraded in this process, potentially vital genetic code would be lost. Telomeres are non-coding, repetitive sequences located at the termini of linear chromosomes to act as buffers for those coding sequences further behind. They "cap" the end-sequences for a protection and are progressively degraded in the process of DNA replication.

The "end replication problem" is exclusive to linear chromosomes as circular chromosomes do not have ends lying without reach of DNA-polymerases. Most prokaryotes, relying on circular chromosomes, accordingly do not possess telomeres.[7] A small fraction of bacterial chromosomes, however, are linear and possess telomeres, which are very different from those of the eukaryotic chromosomes in structure and function. The known structures of bacterial telomeres take the form of proteins bound to the ends of linear chromosomes, or hairpin loops of single-stranded DNA at the ends of the linear chromosomes.[8]

At the 3'-end of the telomere there is a 300 base pair overhang which can invade the double-stranded portion of the telomere forming a structure known as a T-loop. This loop is analogous to a knot, which stabilizes the telomere, and prevents the telomere ends from being recognized as breakpoints by the DNA repair machinery. Should non-homologous end joining occur at the telomeric ends, chromosomal fusion would result. The T-loop is maintained by several proteins, collectively referred to as the shelterin complex. In humans, the shelterin complex consists of six proteins identified as TRF1, TRF2, TIN2, POT1, TPP1, and RAP1.[9] In many species, the sequence repeats are enriched in guanine, e.g. TTAGGG in vertebrates,[10] which allows the formation of G-quadruplexes, a special conformation of DNA involving non-Watson-Crick base pairing. There are different subtypes depending on the involvement of single- or double-stranded DNA, among other things. There is evidence for the 3'-overhang in ciliates (that possess telomere repeats similar to those found in vertebrates) to form such G-quadruplexes that accommodate it, rather than a T-loop. G-quadruplexes present an obstacle for enzymes like DNA-polymerases and are thus thought to be involved in the regulation of replication and transcription.[11]

Telomerase

Many organisms have an enzyme called telomerase, which carries out the task of adding repetitive nucleotide sequences to the ends of the DNA. Telomerase replenishes the telomere cap. In most multicellular eukaryotic organisms, telomerase is active only in germ cells, some types of stem cells such as embryonic stem cells, and certain white blood cells. Telomerase can be reactivated and telomeres reset back to an embryonic state by somatic cell nuclear transfer.[12] The steady shortening of telomeres with each replication in somatic cells may have a role in senescence[13] and in the prevention of cancer.[14][15] This is because the telomeres act as a sort of time-delay fuse, eventually running out after a certain number of cell divisions and resulting in the eventual loss of vital genetic information from the cell's chromosome with future divisions.[16]

In somatic cells, the activity of telomerase, a reverse transcriptase that can elongate telomeric repeats, is usually diminished after birth so that the telomere length is gradually shortened with cell divisions, and triggers cellular senescence. In embryonic stem cells, telomerase is activated and maintains telomere length and cellular immortality; however, the level of telomerase activity is low or absent in the majority of stem cells regardless of their proliferative capacity. Thus, even in stem cells, except for embryonal stem cells and cancer stem cells, telomere shortening occurs during replicative ageing, possibly at a slower rate than that in normal somatic cells. Although telomerase activity is diminished in non-proliferating sperms and ova, it is highly activated after fertilisation and maintained in ES cells and germ cells for the next generation. In the developmental stage, telomerase activity gradually decreases and diminishes in most somatic cells after birth. In adult stem cells, the level of telomerase activity is low or undetectable, and upregulated in committed progenitor cells which have high reproducible activity in each tissue but insufficient to stably maintain their telomere length. Thus, normal stem cells are considered to be mortal and finally senesce by telomere shortening. Cancer stem cells can be derived from normal stem cells, progenitor cells, or possibly somatic cells and might be immortal, having the capacity of indefinite self-renewal and proliferation. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360127/).

Length

Telomere length varies greatly between species, from approximately 300 base pairs in yeast[17] to many kilobases in humans, and usually is composed of arrays of guanine-rich, six- to eight-base-pair-long repeats. Eukaryotic telomeres normally terminate with 3′ single-stranded-DNA overhang, which is essential for telomere maintenance and capping. Multiple proteins binding single- and double-stranded telomere DNA have been identified.[18] These function in both telomere maintenance and capping. Telomeres form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle, stabilized by telomere-binding proteins.[19] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA, and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.[20]

Role in the cell cycle

Telomere shortening in humans can induce replicative senescence, which blocks cell division. This mechanism appears to prevent genomic instability and development of cancer in human aged cells by limiting the number of cell divisions. However, shortened telomeres impair immune function that might also increase cancer susceptibility.[21] If telomeres become too short, they have the potential to unfold from their presumed closed structure. The cell may detect this uncapping as DNA damage and then either stop growing, enter cellular old age (senescence), or begin programmed cell self-destruction (apoptosis) depending on the cell's genetic background (p53 status). Uncapped telomeres also result in chromosomal fusions. Since this damage cannot be repaired in normal somatic cells, the cell may even go into apoptosis. Many aging-related diseases are linked to shortened telomeres. Organs deteriorate as more and more of their cells die off or enter cellular senescence.

Oxidative damage

Apart from the end replication problem, in vitro studies have shown that telomeres accumulate damage due to oxidative stress and that oxidative stress-mediated DNA damage has a major influence on telomere shortening in vivo. There is a multitude of ways in which oxidative stress, mediated by reactive oxygen species (ROS), can lead to DNA damage; however, it is yet unclear whether the elevated rate in telomeres is brought about by their inherent susceptibility or a diminished activity of DNA repair systems in these regions.[22] Despite widespread agreement of the findings, widespread flaws regarding measurement and sampling have been pointed out; for example, a suspected species and tissue dependency of oxidative damage to telomeres is said to be insufficiently accounted for.[23] Population-based studies have indicated an interaction between anti-oxidant intake and telomere length. In the Long Island Breast Cancer Study Project (LIBCSP), authors found a moderate increase in breast cancer risk among women with the shortest telomeres and lower dietary intake of beta carotene, vitamin C or E.[24] These results [25] suggest that cancer risk due to telomere shortening may interact with other mechanisms of DNA damage, specifically oxidative stress.

Association with aging

Telomere shortening is associated with aging, mortality and aging-related diseases. Normal aging is associated with telomere shortening in both humans and mice, and studies on genetically modified animal models suggest causal links between telomere erosion and aging.[26] However, it is not known whether short telomeres are just a symptom of senescence or if they themselves contribute to the progression of the aging process.[27]

The age of a father plays a role in the length of a child's telomeres, which has evolutionary implications. Although leukocyte telomeres shorten with age, sperm telomeres lengthen with age. Shorter telomeres are theorized to impose lower energy costs (due to less replication) but also have immune system-related and other aging- and disease-related costs, so the effect of paternal age on telomere length might be an adaptation to increase the chances that the child will be fit for the environment they're born into.[28][29]

Potential effect of psychological stress

Meta-analyses found that increased perceived psychological stress was associated with a small decrease in telomere length—but that these associations attenuate to no significant association when accounting for publication bias. The literature concerning telomeres as integrative biomarkers of exposure to stress and adversity is dominated by cross-sectional and correlational studies, which makes causal interpretation problematic.[25][30] A 2020 review argued that the relationship between psychosocial stress and telomere length appears strongest for stress experienced in utero or early life.[31]

Lengthening

The phenomenon of limited cellular division was first observed by Leonard Hayflick, and is now referred to as the Hayflick limit.[32][33] Significant discoveries were subsequently made by a group of scientists organized at Geron Corporation by Geron's founder Michael D. West, that tied telomere shortening with the Hayflick limit.[34] The cloning of the catalytic component of telomerase enabled experiments to test whether the expression of telomerase at levels sufficient to prevent telomere shortening was capable of immortalizing human cells. Telomerase was demonstrated in a 1998 publication in *Science* to be capable of extending cell lifespan, and now is well-recognized as capable of immortalizing human somatic cells.[35]

It is becoming apparent that reversing shortening of telomeres through temporary activation of telomerase may be a potent means to slow aging. The reason that this would extend human life is because it would extend the Hayflick limit. Three routes have been proposed to reverse telomere shortening: drugs, gene therapy, or metabolic suppression, so-called torpor/hibernation. So far these ideas have not been proven in humans, but it has been demonstrated that telomere shortening is reversed in hibernation and aging is slowed (Turbill, *et al.* 2012 & 2013) and that hibernation prolongs life-span (Lyman *et al.* 1981). It has also been demonstrated that telomere extension has successfully reversed some signs of aging in laboratory mice [36][37] and the nematode worm species *Caenorhabditis elegans*.[38] It has been hypothesized that longer telomeres and especially telomerase activation might cause increased cancer (Weinstein and Ciszek, 2002[39]). However, longer telomeres might also protect against cancer, because short telomeres are associated with cancer. It has also been suggested that longer telomeres might cause increased energy consumption.[21]

Techniques to extend telomeres could be useful for tissue engineering, because they might permit healthy, noncancerous mammalian cells to be cultured in amounts large enough to be engineering materials for biomedical repairs.

Two studies on long-lived seabirds demonstrate that the role of telomeres is far from being understood. In 2003, scientists observed that the telomeres of Leach's storm-petrel (*Oceanodroma leucorhoa*) seem to lengthen with chronological age, the first observed instance of such behaviour of telomeres.[40] In 2006, Juola *et al.*[41] reported that in another unrelated, long-lived seabird species, the great frigatebird (*Fregata minor*), telomere length did decrease until at least c. 40 years of age (i.e. probably over the entire lifespan), but the speed of decrease slowed down massively with increasing ages, and that rates of telomere length decrease varied strongly between individual birds. They concluded that in this species (and probably in frigatebirds and their relatives in general), telomere length could not be used to determine a bird's age sufficiently well. Thus, it seems that there is much more variation in the behavior of telomere length than initially believed.

Furthermore, Gomes *et al.* found, in a study of the comparative biology of mammalian telomeres, that telomere length of different mammalian species correlates inversely, rather than directly, with lifespan, and they concluded that the contribution of telomere length to lifespan remains controversial.[42] Harris *et al.* found little evidence that, in humans, telomere length is a significant biomarker of normal aging with respect to important cognitive and physical abilities.[43] Gilley and Blackburn tested whether cellular senescence in paramecium is caused by telomere shortening, and found that telomeres were not shortened during senescence.[44]

Sequences

Known, up-to-date telomere nucleotide sequences are listed in Telomerase Database website.

Some known telomere nucleotide sequences

Group	Organism	Telomeric repeat (5' to 3' toward the end)
Vertebrates	Human, mouse, *Xenopus*	TTAGGG
Filamentous fungi	*Neurospora crassa*	TTAGGG
Slime moulds	*Physarum*, *Didymium*	TTAGGG
	Dictyostelium	AG(1-8)
Kinetoplastid protozoa	*Trypanosoma*, *Crithidia*	TTAGGG
Ciliate protozoa	*Tetrahymena*, *Glaucoma*	TTGGGG
	Paramecium	TTGGG(T/G)
	Oxytricha, *Stylonychia*, *Euplotes*	TTTTGGGG
Apicomplexan protozoa	*Plasmodium*	TTAGGG(T/C)
Higher plants	*Arabidopsis thaliana*	TTTAGGG
	Cestrum elegans	TTTTTTAGGG[45]
	Allium	CTCGGTTATGGG[46]
	Green algae *Chlamydomonas*	TTTTAGGG
Insects	*Bombyx mori*	TTAGG
Roundworms	*Ascaris lumbricoides*	TTAGGC
Fission yeasts	*Schizosaccharomyces pombe*	TTAC(A)(C)G(1-8)
Budding yeasts	*Saccharomyces cerevisiae*	TGTGGGTGTGGTG (from RNA template) or G(2-3)(TG)(1-6)T (consensus)

	Saccharomyces castellii	TCTGGGTG
	Candida glabrata	GGGGTCTGGGTGCTG
	Candida albicans	GGTGTACGGATGTCTAACTTCTT
	Candida tropicalis	GGTGTA[C/A]GGATGTCACGATCATT
	Candida maltosa	GGTGTACGGATGCAGACTCGCTT
	Candida guillermondii	GGTGTAC
	Candida pseudotropicalis	GGTGTACGGATTTGATTAGTTATGT
	Kluyveromyces lactis	GGTGTACGGATTTGATTAGGTATGT

Telomere sequences

This page contains the major DNA tandem repeat sequence found within the telomere structures. Each sequence is referenced by original literature citations that are linked to the published online journal. The few species that do not utilize telomerase, certain insects, have the method of elongation listed in place of the tandem repeat. Most telomeric repeats are only 6 to 8 nucleotides, however several yeast species have irregular repeats that range from 6 to 26 nucleotides and contain other variant repeats.

Vertebrates	Sequences	References
vertebrate sp.	TTAGGG	Meyne *et al*, 1989

	Invertebrates	Sequences	References
	Ciona sp.(sea squirt)	TTAGGG	
	Ciona savignyi (sea squirt)	TTAGGG	
	Oikopleura dioica (sea squirt)	TTAGGG	Schulmeister *et al*, 2007
	Botryllus schlosseri (star ascidian)	TTAGGG	Laird and Weissman, 2004
	Strongylocentrotus purpuratus (purple sea urchin)	TTAGGG	Sinclair *et al*, 2007
	Donax trunculus (wedgeshell clam)	TTAGGG	Sinclair *et al*, 2007
	Argopecten irradians (bay scallop)	TTAGGG	Sinclair *et al*, 2007
	Cassiopeidae sp. (jellyfish)	TTAGGG	Ojimi *et al*, 2008
	Gammarus pulex (freshwater shrimp)	TTAGG	Sahara *et al*, 1999
beetles	Stegobium paniceum (drugstore beetle)	TTAGG	Frydrychová *et al*, 2004
	Agrilus viridis (beetle)	TTAGG	Frydrychová *et al*, 2004
	Arhopalus coreanus (beetle)	TTAGG	Okazaki *et al*, 1993
	Spondylis buprestoides (longhorn beetle)	TTAGG	Okazaki *et al*, 1993
	Leptinotarsa decemlineata (Colorado potato beetle)	TTAGG	Frydrychová *et al*, 2004
	Ips typographus (Spruce bark beetle)	TTAGG	Sahara *et al*, 1999
	Graphoderus cinereus (beetle)	TTAGG	Frydrychová *et al*, 2004
	Ampedus sanguineus (beetle)	TTAGG	Frydrychová *et al*, 2004
	Diacanthous undosus (beetle)	TTAGG	Okazaki *et al*, 1993
	Melanotus legatus (click beetle)	TTAGG	Okazaki *et al*, 1993

	Mylabris sp.	TCAGG	Mravinac *et al*, 2011
	Typhaea stercorea	TCAGG	Mravinac *et al*, 2011
	Silpha obscura (beetle)	TTAGG	Frydrychová *et al*, 2004
	Oryzaephilus surinamensis (grain beetle)	TTAGG	Frydrychová *et al*, 2004
	Palorus ratzeburgii (small-eyed flour beetle)	TCAGG	Mravinac *et al*, 2011
	Palorus subdepressus	TCAGG	Mravinac *et al*, 2011
	Palorus genalis	TCAGG	Mravinac *et al*, 2011
	Palorus ficicola	TCAGG	Mravinac *et al*, 2011
	Pimelia elevata	TCAGG	Mravinac *et al*, 2011
	Pimelia criba	TCAGG	Mravinac *et al*, 2011
	Pimelia monticola	TCAGG	Mravinac *et al*, 2011
	Tenebrio molitor (yellow mealworm)	TCAGG	Mravinac *et al*, 2011
	Tenebrio obscurus	TCAGG	Mravinac *et al*, 2011
	Tribolium castaneum (red flour beetle)	TCAGG	Tribolium Gen. Seq. Con., 2008 Osanai *et al*, 2006
	Tribolium freemani	TCAGG	Mravinac *et al*, 2011
	Tribolium confusum	TCAGG	Mravinac *et al*, 2011
	Tribolium madens	TCAGG	Mravinac *et al*, 2011
	Tribolium audax	TCAGG	Mravinac *et al*, 2011
	Tribolium brevicornis	TCAGG	Mravinac *et al*, 2011
	Tribolium anaphe	TCAGG	Mravinac *et al*, 2011
	Tribolium destructor	TCAGG	Mravinac *et al*, 2011
flies	Chironomus tentans (fly)	satellite sequence	Nielsen *et al*, 1993
	Anopheles gambiae (African malaria mosquito)	unequal recombination	Roth et al, 1997
	Drosophila melanogaster (fruit fly)	retrotransposons	Biessmann *et al*, 1990
	Drosophila virilis (fly)	retrotransposons satellite sequence	Frydrychová *et al*, 2004
	Apis mellifera (honey bee)	TTAGG	Sahara *et al*, 1999
	Manica yessensis (ant)	TTAGG	Okazaki *et al*, 1993
	Myrmecia sp. (ant)	TTAGG	Meyne *et al*, 1995
	Tapinoma nigerrimum (ant)	TTAGG	Frydrychová *et al*, 2004
Lepidopterans	Bombyx mori (domestic silkworm)	TTAGG	Okazaki *et al*, 1993
	Bombyx mandarina (wild silkworm)	TTAGG	Okazaki *et al*, 1993
	Mamestra brassicae (cabbage moth)	TTAGG	Frydrychová *et al*, 2004
	Papilio xuthus (butterfly)	TTAGG	Frydrychová *et al*, 2004
	Ephestia kuehniella (Mediterranean flour moth)	TTAGG	Sahara *et al*, 1999
	Galleria mellonella (wax moth)	TTAGG	Sahara *et al*, 1999
	Antheraea pernyi (Chinese oak silkmoth)	TTAGG	Okazaki *et al*, 1993
	Antheraea yamamai (Japanese oak silkmoth)	TTAGG	Frydrychová *et al*, 2004

	Samia cynthia ricini (Indian silkmoth)	TTAGG	Okazaki *et al*, 1993
	Agrius convolvuli (morning glory sphinx moth)	TTAGG	Frydrychová *et al*, 2004
[redacted]			
	Sialis lutaria (alderfly)	TTAGG	Frydrychová *et al*, 2004
[redacted]			
	Stenopsyche japonica (caddisfly)	TTAGG	Okazaki *et al*, 1993
	Limnephilus decipiens (caddisfly)	TTAGG	Frydrychová *et al*, 2004
[redacted]			
	Protidricerus japonicus (owlfly)	TTAGG	Frydrychová *et al*, 2004
[redacted]			
	Periplaneta fuliginosa (dusky-brown cockroach)	TTAGG	Okazaki *et al*, 1993
[redacted]			
	Hodotermopsis japonicus (termite)	TTAGG	Okazaki *et al*, 1993
[redacted]			
	Locusta migratoria (migratory locust)	TTAGG	Okazaki *et al*, 1993
	Diestrammena japonica (camel cricket)	TTAGG	Okazaki *et al*, 1993
[redacted]			
nematodes	Ascaris lumbricoides	TTAGGC	Müller *et al*, 1991
	Ascaris suum	TTAGGC	Teixeria *et al*, 2005
	Parascaris univalens	TTGCA	Teschke *et al*, 1991
	Caenorhabditis elegans	TTAGGC	Cangiano *et al*, 1993

	Fungi	**Sequences**	**References**
	Schizosaccharomyces pombe (fission yeast)	G2–8TTAC(A)	Joseph *et al*, 2007 Murray *et al*, 1986
[redacted]			
Saccharomycotina	Saccharomyces cerevisiae (baker's yeast)	T(G)2-3(TG)1-6	Shampay *et al*, 1984 McEachern and Blackburn, 1994
	Saccharomyces bayanus	T(G)2-3(TG)1-6	Teixeria *et al*, 2005
	Saccharomyces paradoxus	T(G)2-3(TG)1-6	Teixeria *et al*, 2005
	Saccharomyces mikatae	T(G)2-3(TG)1-6	Teixeria *et al*, 2005
	Saccharomyces exiguus	T(G)2-3(TG)1-6	Cohn *et al*, 1998
	Saccharomyces dairenensis	TCTGGG(TG)1-3 TCTGGG	Cohn *et al*, 1998
	Saccharomyces castellii	TCTGGG(TG)1-4	Cohn *et al*, 1995
	Saccharomyces kluyveri	GGGTGGACATGCGTACTGTGAGGTCT	Cohn *et al*, 1998
	Kluyveromyces lactis	ACGGATTTGATTAGGTATGTGGTGT	McEachern and Blackburn, 1994
	Candida albicans	ACGGATGTCTAACTTCTTGGTGT	McEachern and Blackburn, 1994
	Candida glabrata	CTGGGTGCTGTGGGGT	McEachern and Blackburn, 1994

	Candida guillermondii	ACTGGTGT	McEachern and Blackburn, 1994
	Candida maltosa	ACGGATGCAGACTCGCTTGGTGT	McEachern and Blackburn, 1994
	Candida metapsilosis	GGTTAGGATGTCCAAAGTATTGA	Gunisova *et al*, 2009
	Candida orthopsilosis	GGTTAGGATGTAGACAATACTGC	Gunisova *et al*, 2009
	Candida parapsilosis	GGTCCGGATGTTGATTATACTGA	Gunisova *et al*, 2009
	Candida pseudotropicalis	ACGGATTTGATTAGTTATGTGGTGT	McEachern and Blackburn, 1994
	Candida sojae	TGTAAGGATGCAAAACCGCTATTCG	Gunisova *et al*, 2009
	Candida tropicalis	A[C/A]GGATGTCACGATCATTGGTGT	Gunisova *et al*, 2009
		AAGGATGTCACGATCATTGGTGT	McEachern and Blackburn, 1994
	Debaryomyces hansenii	ATGTTGAGGTGTAGGG	Lépingle *et al*, 2000
	Ashbya gossypii (Eremothecium gossypii)	GTGTGGTGTATGGGTCTCTCAGCG	Dietrich *et al*, 2004
	Lodderomyces elongisporus	CGGTGTAAGGATGCACTTGAAACT	Gunisova *et al*, 2009
	Pichia guilliermondii	ACTGGTGT	Teixeria *et al*, 2005
	Pichia stipitis	GGATCTTTTCACGTCTTGCGGTA	Jeffries et al, 2007
	Yarrowia lipolytica	GGACGATTG	Teixeria *et al*, 2005
	Clavispora lusitaniae	TCTTTAGGGAGGTACTGATGT	Gunisova *et al*, 2009
Pezizomycotina	Aspergillus fumigatus	TTAGGG	Nierman *et al*, 2005
	Aspergillus oryzae	TTAGGGTCAACA	Kusumoto *et al*, 2003
	Aspergillus nidulans (Emericella nidulans)	TTAGGG	Bhattacharyya *et al*, 1997
	Histoplasma capsulatum	TTAGGG	Woods *et al*, 1992
	Cladosporium fulvum	TTAGGG	Coleman *et al*, 1993
	Magnaporthe grisea (rice blast fungus)	TTAGGG	Teixeria *et al*, 2005
	Podospora anserina	TTAGGG	Javerzat *et al*, 1993
	Neurospora crassa	TTAGGG	Schechtman, 1990
	Cryptococcus neoformans (Filobasidiella neoformans)	TTA(G)4-6	Edman, 1992
	Encephalitozoon cuniculi	G[A/G]GCCT[C/T]CT	Peyret *et al*, 2001
		GAGCCTTGTTT	
		GAGACGCAGTGTTGCCAGGATG	
	Rhizopus oryzae	TTGTGG	Ma *et al*, 2009

Amoeba	Sequences	References
Dictyostelium discoideum	A(G)1-8	Emery *et al*, 1981
Physarum polycephalum	TTAGGG	Forney *et al*, 1987
Didymium iridis	TTAGGG	Forney *et al*, 1987

	Plants	Sequences	References
	plants sp.	TTTAGGG	Cox *et al*, 1993 Fuchs *et al*, 1995
eudicots	Nicotiana tabacum (common tobacco)	TTAGGG	Weiss *et al*, 2002
	Solanum lycopersicum (tomato)	TT[T/A]GGG	Ganal *et al*, 1991
	Strombosia pustulata (Italian olive ash)	TTTTAGGG	Teixeria *et al*, 2005
	Arabidopsis thaliana (thale cress)	TTTAGGG	Richards *et al*, 1988
	Aloe sp.	TTAGGG	Weiss *et al*, 2002
	Hyacinthella dalmatica	TTAGGG	Puizina *et al*, 2003
	Othocallis siberica (Siberian squill)	TTAGGG	Weiss-Schneeweiss *et al*, 2004

Algae	Sequences	References
Cyanidioschyzon merolae (red algae)	AATGGGGGG	Nozaki *et al*, 2007
Chlamydomonas reinhardtii (green alga)	TTTTAGGG	Petracek *et al*, 1990

	Ciliates	Sequences	References
Oligohymenophorea	Glaucoma chattoni	TTGGGG	Katzen *et al*, 1981
	Tetrahymena thermophila	TTGGGG	Blackburn *et al*, 1978
	Paramecium tetraurelia	TT[T/G]GGG	Forney *et al*, 1988
	Paramecium primaurelia	TT[T/G]GGG	Forney *et al*, 1988
	Paramecium multimicronucleatum	TT[T/G]GGG	Forney *et al*, 1988
	Paramecium caudatum	TT[T/G]GGG	Forney *et al*, 1988
Spirotrich	Euplotes aediculatus	TTTTGGGG	Klobutcher *et al*, 1981
	Euplotes eurystomus	TTTTGGGG	Klobutcher *et al*, 1981
	Euplotes crassus	TTTTGGGG	Klobutcher *et al*, 1981
	Oxytricha nova (Sterkiella nova)	TTTTGGGG	Klobutcher *et al*, 1981
	Oxytricha trifallax (Sterkiella histriomuscorum)	TTTTGGGG	Klobutcher *et al*, 1981

Other Protists	Sequences	References
Plasmodium falciparum (human parasite)	TT[T/C]AGGG	Vernick *et al*, 1988
Plasmodium berghei (rodent parasite)	TT[T/C]AGGG	Ponzi *et al*, 1985
Theileria annulata	TTTTAGGG	Sohanpal *et al*, 1995
Cryptosporidium parvum	TTTAGG	Liu *et al*, 1998
Giardia lamblia	TTAGG	Morrison *et al*, 2007
Giardia intestinalis	TAGGG	Le Blancq *et al*, 1991
Leishmania major	TTAGGG	Teixeria *et al*, 2005
Trypanosoma brucei	TTAGGG	Blackburn *et al*, 1984

http://telomerase.asu.edu/sequences_telomere.html

Research on disease risk

Telomeres are critical for maintaining genomic integrity and may be factors for age-related diseases.[47] Laboratory studies show that telomere dysfunction or shortening is commonly acquired due process of cellular aging and tumor development.[47][48] Short telomeres can lead to genomic instability, chromosome loss and the formation of non-reciprocal translocations; and telomeres in tumor cells and their precursor lesions are significantly shorter than surrounding normal tissue.[49][50]

Observational studies have found shortened telomeres in many types of experimental cancers.[51] In addition, people with cancer have been found to possess shorter leukocyte telomeres than healthy controls.[52] Recent meta-analyses suggest 1.4 to 3.0 fold increased risk of cancer for those with the shortest vs. longest telomeres.[53][54] However, the increase in risk varies by age, sex, tumor type, and differences in lifestyle factors.[51]

Measurement

Several techniques are currently employed to assess average telomere length in eukaryotic cells. One method is the Terminal Restriction Fragment (TRF) southern blot.[55][56] A Real-Time PCR assay for telomere length involves determining the Telomere-to-Single Copy Gene (T/S) ratio, which is demonstrated to be proportional to the average telomere length in a cell.[57]

Tools have also been developed to estimate the length of telomere from whole genome sequencing (WGS) experiments. Amongst these are TelSeq,[58] telomere Cat[59] and telomereHunter.[60] Length estimation from WGS typically works by differentiating telomere sequencing reads and then inferring the length of telomere that produced that number of reads. These methods have been shown to correlate with preexisting methods of estimation such as PCR and TRF. Flow-FISH is used to quantify the length of telomeres in human white blood cells. A semi-automated method for measuring the average length of telomeres with Flow FISH was published in Nature Protocols in 2006.[61]

While multiple companies offer telomere length measurement services, the utility of these measurements for widespread clinical or personal use has been questioned.[62][63] Nobel Prize winner Elizabeth Blackburn, who was co-founder of one company, promoted the clinical utility of telomere length measures.[64]

In ectotherms

Most research on telomere length and regulation, and its relationship to cancer and aging, has been performed on mammals, especially humans, which have little or no somatic telomerase production. Ectotherms are significantly more likely than endotherms to have variation in somatic telomerase expression. For instance, in many fish, telomerase occurs throughout the body (and associated with this, telomere length is roughly the same across all its tissue). Studies on ectotherms, and other non-mammalian organisms, show that there is no single universal model of telomere erosion; rather, there is wide variation in relevant dynamics across Metazoa, and even within smaller taxonomic groups these patterns appear diverse. Due to the different reproductive timelines of some ectotherms, selection on disease is relevant for a much larger fraction of these creatures' lives than it is for mammals, so early- and late-life telomere length, and their possible links to cancer, seem especially important in these species from a life history theory point of view.[65]

References

[1]. *^ Mender I, Shay JW (November 2015). "Telomerase Repeated Amplification Protocol (TRAP)". Bio-Protocol.* ***5*** *(22): e1657. doi:10.21769/bioprotoc.1657. PMC 4863463. PMID 27182535.*

[2]. *^ Blackburn EH, Gall JG (March 1978). "A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in Tetrahymena". Journal of Molecular Biology.* ***120*** *(1): 33–53. doi:10.1016/0022-2836(78)90294-2. PMID 642006.*

[3]. *^ "Elizabeth H. Blackburn, Carol W. Greider, Jack W. Szostak: The Nobel Prize in Physiology or Medicine 2009". Nobel Foundation. 2009-10-05. Retrieved 2012-06-12.*

[4]. *^ "Barbara McClintock: The Nobel Prize in Physiology or Medicine 1983". Nobel Foundation. 1983. Retrieved 10 March 2018.*

[5]. *^ Olovnikov AM (September 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*** *(1): 181–90. doi:10.1016/0022-5193(73)90198-7. PMID 4754905.*

[6]. *^ Chow TT, Zhao Y, Mak SS, Shay JW, Wright WE (June 2012). "Early and late steps in telomere overhang processing in normal human cells: the position of the final RNA primer drives telomere shortening". Genes & Development.* ***26*** *(11): 1167–78.*

doi:10.1101/gad.187211.112. PMC 3371406. PMID 22661228.

[7]. ^ Nelson DL, Lehninger AL, Cox MM (2008). Lehninger principles of biochemistry (5th ed.). New York: W.H. Freeman. ISBN 9780716771081. OCLC 191854286.

[8]. ^ Maloy S (July 12, 2002). "Bacterial Chromosome Structure". Retrieved 2008-06-22.

[9]. ^ Martínez P, Blasco MA (October 2010). "Role of shelterin in cancer and aging". Aging Cell. **9** (5): 653–66. doi:10.1111/j.1474-9726.2010.00596.x. PMID 20569239.

[10]. ^ Meyne J, Ratliff RL, Moyzis RK (September 1989). "Conservation of the human telomere sequence (TTAGGG)n among vertebrates". Proceedings of the National Academy of Sciences of the United States of America. **86** (18): 7049–53. Bibcode: 1989PNAS...86.7049M. doi:10.1073/pnas.86.18.7049. PMC 297991. PMID 2780561.

[11]. ^ Lipps HJ, Rhodes D (August 2009). "G-quadruplex structures: in vivo evidence and function". Trends in Cell Biology. **19** (8): 414–22. doi:10.1016/j.tcb.2009.05.002. PMID 19589679.

[12]. ^ Lanza RP, Cibelli JB, Blackwell C, Cristofalo VJ, Francis MK, Baerlocher GM, et al. (April 2000). "Extension of cell life-span and telomere length in animals cloned from senescent somatic cells". Science. **288** (5466): 665–9. Bibcode: 2000Sci...288..665L. doi:10.1126/science.288.5466.665. PMID 10784448. S2CID 37387314.

[13]. ^ Whittemore, Kurt; Vera, Elsa; Martínez-Nevado, Eva; Sanpera, Carola; Blasco, Maria A. (2019). "Telomere shortening rate predicts species life span". Proceedings of the National Academy of Sciences. **116** (30): 15122–15127. doi:10.1073/pnas.1902452116. ISSN 0027-8424.

[14]. ^ Shay JW, Wright WE (May 2005). "Senescence and immortalization: role of telomeres and telomerase". Carcinogenesis. **26** (5): 867–74. doi:10.1093/carcin/bgh296. PMID 15471900.

[15]. ^ Wai LK (July 2004). "Telomeres, telomerase, and tumorigenesis--a review". Med Gen Med. **6** (3): 19. PMC 1435592. PMID 15520642.

[16]. ^ Greider CW (August 1990). "Telomeres, telomerase and senescence". BioEssays. **12** (8): 363–9. doi:10.1002/bies.950120803. PMID 2241933. S2CID 11920124.

[17]. ^ Shampay J, Szostak JW, Blackburn EH (1984). "DNA sequences of telomeres maintained in yeast". Nature. **310** (5973): 154–7. Bibcode:1984 Natur.310..154S. doi:10.1038/310154a0. PMID 6330571. S2CID 4360698.

[18]. ^ Williams TL, Levy DL, Maki-Yonekura S, Yonekura K, Blackburn EH (November 2010). "Characterization of the yeast telomere nucleoprotein core: Rap1 binds independently to each recognition site". The Journal of Biological Chemistry. **285** (46): 35814–24. doi:10.1074/jbc.M110.170167. PMC 2975205. PMID 20826803.

[19]. ^ Griffith JD, Comeau L, Rosenfield S, Stansel RM, Bianchi A, Moss H, de Lange T (May 1999). "Mammalian telomeres end in a large duplex loop". Cell. **97** (4): 503–14. doi:10.1016/S0092-8674(00)80760-6. PMID 10338214. S2CID 721901.

[20]. ^ Burge S, Parkinson GN, Hazel P, Todd AK, Neidle S (2006). "Quadruplex DNA: sequence, topology and structure". Nucleic Acids Research. **34** (19): 5402–15. doi:10.1093/nar/gkl655. PMC 1636468. PMID 17012276.

[21]. ^ Jump up to:[a] [b] Eisenberg DT (2011). "An evolutionary review of human telomere biology: the thrifty telomere hypothesis and notes on potential adaptive paternal effects". American Journal of Human Biology. **23** (2): 149–67. doi:10.1002/ajhb.21127. PMID 21319244. S2CID 5540894.

[22]. ^ Barnes R, Fouquerel E, Opresko P (2019). "The impact of oxidative DNA damage and stress on telomere homeostasis". Mechanisms of Ageing and Development. **177**: 37–45. doi:10.1016/j.mad.2018.03.013. PMC 6162185.

[23]. ^ Reichert S, Stier A (December 2017). "Does oxidative stress shorten telomeres in vivo? A review". Biology Letters. **13** (12): 20170463. doi:10.1098/rsbl.2017.0463. PMC 5746531. PMID 29212750.

[24]. ^ Shen J, Gammon MD, Terry MB, Wang Q, Bradshaw P, Teitelbaum SL, et al. (April 2009). "Telomere length, oxidative damage, antioxidants and breast cancer risk". International Journal of Cancer. **124** (7): 1637–43. doi:10.1002/ijc.24105. PMC 2727686. PMID 19089916.

[25]. ^ Jump up to:[a] [b] Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, Khazeni N (May 2016). "Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field". Brain, Behavior, and Immunity. **54**:

158–169. doi:10.1016/j.bbi.2016.02.002. PMC 5590630. PMID 26853993.

[26]. ^ López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (June 2013). "The hallmarks of aging". Cell. **153** (6): 1194–217. doi:10.1016/j.cell.2013.05.039. PMC 3836174. PMID 23746838.

[27]. ^ Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P (2017). Molecular Biology of the Cell (Sixth ed.). Garland Science. pp. 1230–1233. ISBN 978-1-315-73536-8.

[28]. ^ Eisenberg DT (17 December 2010). "An evolutionary review of human telomere biology: the thrifty telomere hypothesis and notes on potential adaptive paternal effects". American Journal of Human Biology. **23** (2): 149–67. doi:10.1002/ajhb.21127. PMID 21319244. S2CID 5540894.

[29]. ^ Aston KI, Hunt SC, Susser E, Kimura M, Factor-Litvak P, Carrell D, Aviv A (November 2012). "Divergence of sperm and leukocyte age-dependent telomere dynamics: implications for male-driven evolution of telomere length in humans". Molecular Human Reproduction. **18** (11): 517–22. doi:10.1093/molehr/gas028. PMC 3480822. PMID 22782639.

[30]. ^ Pepper GV, Bateson M, Nettle D (August 2018). "Telomeres as integrative markers of exposure to stress and adversity: a systematic review and meta-analysis". Royal Society Open Science. **5** (8): 180744. Bibcode:2018RSOS....580744P. doi:10.1098/rsos.180744. PMC 6124068. PMID 30225068.

[31]. ^ Rentscher KE, Carroll JE, Mitchell C (April 2020). "Psychosocial Stressors and Telomere Length: A Current Review of the Science". Annual Review of Public Health. **41**: 223–245. doi:10.1146/annurev-publhealth-040119-094239. PMID 31900099.

[32]. ^ Hayflick L, Moorhead PS (December 1961). "The serial cultivation of human diploid cell strains". Experimental Cell Research. **25** (3): 585–621. doi:10.1016/0014-4827(61)90192-6. PMID 13905658.

[33]. ^ Hayflick L (March 1965). "The limited in vitro lifetime of human diploid cell strains". Experimental Cell Research. **37** (3): 614–36. doi:10.1016/0014-4827(65)90211-9. PMID 14315085.

[34]. ^ Feng J, Funk WD, Wang SS, Weinrich SL, Avilion AA, Chiu CP, et al. (September 1995). "The RNA component of human telomerase". Science. **269** (5228): 1236–41. Bibcode:1995Sci...269.1236F. doi:10.1126/science.7544491. PMID 7544491. S2CID 9440710.

[35]. ^ Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, et al. (January 1998). "Extension of life-span by introduction of telomerase into normal human cells". Science. **279** (5349): 349–52. Bibcode:1998Sci...279..349B. doi:10.1126/science.279.5349.349. PMID 9454332. S2CID 35667874.

[36]. ^ Sample I (November 28, 2010). "Harvard scientists reverse the ageing process in mice – now for humans". The Guardian. London.

[37]. ^ Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, et al. (January 2011). "Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice". Nature. **469**(7328): 102–6. Bibcode:2011Natur.469..102J. doi:10.1038/nature09603. PMC 3057569. PMID 21113150.

[38]. ^ Joeng KS, Song EJ, Lee KJ, Lee J (June 2004). "Long lifespan in worms with long telomeric DNA". Nature Genetics. **36** (6): 607–11. doi:10.1038/ng1356. PMID 15122256.

[39]. ^ Weinstein BS, Ciszek D (May 2002). "The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair". Experimental Gerontology. **37** (5): 615–27. doi:10.1016/S0531-5565(02)00012-8. PMID 11909679. S2CID 12912742.

[40]. ^ Nakagawa S, Gemmell NJ, Burke T (September 2004). "Measuring vertebrate telomeres: applications and limitations"(PDF). Molecular Ecology. **13** (9): 2523–33. doi:10.1111/j.1365-294X.2004.02291.x. PMID 15315667.

[41]. ^ Juola FA, Haussmann MF, Dearborn DC, Vleck CM (July 2006). "Telomere shortening in a long-lived marine bird: cross-sectional analysis and test of an aging tool". The Auk. **123** (3): 775–83. doi:10.1642/0004-8038(2006)123[775:TSIALM]2.0.CO;2. JSTOR 4090554.

[42]. ^ Gomes NM, Ryder OA, Houck ML, Charter SJ, Walker W, Forsyth NR, et al. (October 2011). "Comparative biology of mammalian telomeres: hypotheses on ancestral states and the roles of telomeres in longevity determination". Aging Cell. **10** (5): 761–8. doi:10.1111/j.1474-9726.2011.00718.x. PMC 3387546. PMID 21518243.

[43]. ^ Harris SE, Martin-Ruiz C, von Zglinicki T, Starr JM, Deary IJ (July 2012). "Telomere

length and aging biomarkers in 70-year-olds: the Lothian Birth Cohort 1936". Neurobiology of Aging. **33** (7): 1486.e3–8. doi:10.1016/j.neurobiolaging.2010.11.013. PMID 21194798. S2CID 10309423.

[44]. ^ Gilley D, Blackburn EH (March 1994). "Lack of telomere shortening during senescence in Paramecium". Proceedings of the National Academy of Sciences of the United States of America. **91** (5): 1955–8. Bibcode:1994PNAS...91.1955G. doi:10.1073/pnas.91.5.1955. PMC 43283. PMID 8127914.

[45]. ^ Peška V, Fajkus P, Fojtová M, Dvořáčková M, Hapala J, Dvořáček V, et al. (May 2015). "Characterisation of an unusual telomere motif (TTTTTTAGGG)n in the plant Cestrum elegans (Solanaceae), a species with a large genome". The Plant Journal. **82** (4): 644–54. doi:10.1111/tpj.12839. PMID 25828846.

[46]. ^ Fajkus P, Peška V, Sitová Z, Fulnečková J, Dvořáčková M, Gogela R, et al. (February 2016). "Allium telomeres unmasked: the unusual telomeric sequence (CTCGGTTATGGG)n is synthesized by telomerase". The Plant Journal. **85** (3): 337–47. doi:10.1111/tpj.13115. PMID 26716914. S2CID 206331112.

[47]. ^ Jump up to:[a] [b] Price LH, Kao HT, Burgers DE, Carpenter LL, Tyrka AR (January 2013). "Telomeres and early-life stress: an overview". Biological Psychiatry. **73** (1): 15–23. doi:10.1016/j.biopsych.2012.06.025. PMC 3495091. PMID 22831981.

[48]. ^ Raynaud CM, Sabatier L, Philipot O, Olaussen KA, Soria JC (May 2008). "Telomere length, telomeric proteins and genomic instability during the multistep carcinogenic process". Critical Reviews in Oncology/Hematology. **66** (2): 99–117 doi:10.1016/j.critrevonc.2007.11.006. PMID 18243729.

[49]. ^ Blasco MA, Lee HW, Hande MP, Samper E, Lansdorp PM, DePinho RA, Greider CW (October 1997). "Telomere shortening and tumor formation by mouse cells lacking telomerase RNA". Cell. **91**(1): 25–34. doi:10.1016/s0092-8674(01)80006-4. PMID 9335332. S2CID 13366934.

[50]. ^ Artandi SE, Chang S, Lee SL, Alson S, Gottlieb GJ, Chin L, DePinho RA (August 2000). "Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice". Nature. **406**(6796): 641–5. Bibcode:2000Natur.406..641A. doi:10.1038/35020592. PMID 10949306. S2CID 4420387.

[51]. ^ Jump up to:[a] [b] Armanios M (March 2013). "Telomeres and age-related disease: how telomere biology informs clinical paradigms". The Journal of Clinical Investigation. **123** (3): 996–1002. doi:10.1172/JCI66370. PMC 3673231. PMID 23454763.

[52]. ^ Willeit P, Willeit J, Mayr A, Weger S, Oberhollenzer F, Brandstätter A, et al. (July 2010). "Telomere length and risk of incident cancer and cancer mortality". JAMA. **304** (1): 69–75. doi:10.1001/jama.2010.897. PMID 20606151.

[53]. ^ Ma H, Zhou Z, Wei S, Liu Z, Pooley KA, Dunning AM, et al. (2011). "Shortened telomere length is associated with increased risk of cancer: a meta-analysis". PLOS ONE. **6** (6): e20466. Bibcode:2011PLoSO...620466M. doi:10.1371/journal.pone.0020466. PMC 3112149. PMID 21695195.

[54]. ^ Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA (June 2011). "The association of telomere length and cancer: a meta-analysis". Cancer Epidemiology, Biomarkers & Prevention. **20** (6): 1238–50. doi:10.1158/1055-9965.epi-11-0005. PMC 3111877. PMID 21467229.

[55]. ^ Allshire RC, et al. (June 1989). "Human telomeres contain at least three types of G-rich repeat distributed non-randomly". Nucleic Acids Research. **17** (12): 4611–27. doi:10.1093/nar/17.12.4611. PMC 318019. PMID 2664709.

[56]. ^ Rufer N, et al. (August 1998). "Telomere length dynamics in human lymphocyte subpopulations measured by flow cytometry". Nature Biotechnology. **16** (8): 743–7. doi:10.1038/nbt0898-743. PMID 9702772. S2CID 23833545.

[57]. ^ Cawthon RM (May 2002). "Telomere measurement by quantitative PCR". Nucleic Acids Research. **30** (10): 47e–47. doi:10.1093/nar/30.10.e47. PMC 115301. PMID 12000852.

[58]. ^ Ding Z (2014). "Estimating telomere length from whole genome sequence data". Nucleic Acids Research. **42** (9): e75. doi:10.1093/nar/gku181. PMC 4027178. PMID 24609383.

[59]. ^ Farmery J (2018). "TelomereCat: A ploidy-agnostic method for estimating telomere length from whole genome sequencing data". Scientific Reports. **8** (1): 1300. Bibcode:2018NatSR...8.1300F. doi:10.1038/s4

1598-017-14403-y. PMC 5778012. PMID 29358629.

[60]. ^ *Feuerbach L (2019). "TelomereHunter–in silico estimation of telomere content and composition from cancer genomes". BMC Bioinformatics.* ***20*** *(1): 272. doi:10.1186/s12859-019-2851-0. PMC 6540518. PMID 31138115.*

[61]. ^ *Baerlocher GM, Vulto I, de Jong G, Lansdorp PM (December 2006). "Flow cytometry and FISH to measure the average length of telomeres (flow FISH)". Nature Protocols.* ***1*** *(5): 2365–76. doi:10.1038/nprot.2006.263. PMID 17406480 S2CID 20463557.*

[62]. ^ *Pollack, Andrew (May 18, 2011). "A Blood Test Offers Clues to Longevity". The New York Times.*

[63]. ^ *von Zglinicki T (March 2012). "Will your telomeres tell your future?". BMJ.* ***344****: e1727. doi:10.1136/bmj.e1727. PMID 22415954. S2CID 44594597.*

[64]. ^ *Marchant J (2011). "Spit test offers guide to health". Nature. doi:10.1038/news.2011.330.*

[65]. ^ *Olsson M, Wapstra E, Friesen C (March 2018). "Ectothermic telomeres: it's time they came in from the cold". Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* ***373*** *(1741): 20160449. doi:10.1098/rstb.2016.0449. PMC 5784069. PMID 29335373.*

[66]. Wikipedia. Telomere. https://en.wikipedia.org/wiki/Telomere. 2021.

[67]. http://telomerase.asu.edu/sequences_telomere.html. 2021.

[68]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360127/.

[69]. Google. http://www.google.com. 2021.

[70]. Journal of American Science. http://www.jofamericanscience.org. 2021.

[71]. Life Science Journal. http://www.lifesciencesite.com. 2021.

[72]. http://www.sciencepub.net/nature/0501/10-0247-mahongbao-eternal-ns.pdf.

[73]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. doi:10.7537/marsnsj010103.01. http://www.sciencepub.net/nature/0101/01-ma.pdf.

[74]. Marsland Press. http://www.sciencepub.net. 2021.

[75]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2021.

[76]. Nature and Science. http://www.sciencepub.net/nature. 2021.

[77]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2021.

8/16/2021