Telomeres: implications for aging and evidence for intelligent design

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The complex telomere system in eukaryotic chromosomes eloquently demonstrates a precise well-designed mechanism that interacts with a wide variety of interconnected cell processes and pathways. It regulates gene expression and both cellular and organismal longevity through a unique time-keeping mechanism. The telomere system also contains structural features that protect the linear chromosome ends, making higher forms of cell life possible. In vertebrates, particularly humans, the telomere system is associated with a large number of age-related diseases, cancer, and cell longevity in general. Understanding this system may help to explain some aspects associated with the wide historical variation in human longevity, specifically the disparity of lifespans as described in the biblical record. In addition, the interdependence of the thousands of components related to the telomere system provides an overwhelming case for both irreducible complexity and intelligent design.

The classic proof for the existence of a Creator God, ubiquitous in the natural world, is an apologetic termed the teleological argument*. The famous nineteenth century theologian, William Paley, used this approach in the early 1800s to argue for God's existence. Paley compared the complexity of a mechanical watch to the details of complex biological systems. He reasoned that a watch implies the existence of a watchmaker, so the intricate complexity of biological life, which surpasses that of human-made watches, likewise indicates the existence of a divine creator.[1]

The complexity of a single eukaryotic cell is now known to be far greater than that previously believed true of entire organisms. Our understanding of living organisms, even as late as the early 1900s, was primitive compared to today's knowledge. Paley's watch analogy has now been eloquently documented, especially in the field of molecular and cellular biology.[2–4] One excellent example of the vast complexity of the cell is the telomere system in linear eukaryotic chromosomes.

Telomeres function as protective caps that protect the ends of linear chromosomes (figure 1) from degradation and recombination (fusion) with other chromosomes or DNA fragments.[5] The term 'telomere' was first coined by geneticist Hermann J. Muller from *telos*, Greek for "end", and *meros*, Greek for "part".[6] Muller noticed in his experiments on *Drosophila* (fruit fly) conducted in the 1930s that irradiated chromosomes would break and then fuse, except for end-points, which appeared to be protected from fusion. These findings were subsequently confirmed by Nobel laureate geneticist Barbara McClintock when researching breakage and fusion of maize chromosomes.[7] Modern research on the telomere structure system began with the work of James Watson and Alexy Olovnikov in the early 1970s.[8,9]

Since then, a meteoric rise in understanding the complexities of telomeres and their relation to human health and controlling factors has occurred. A decade ago, Bergman published a comprehensive creationist review on telomeres for technical readers.[10] Since that time, many major discoveries in telomere biology have added more evidence to the irreducible complexity—intelligent design model for biological systems and provided more data to elucidate the mechanisms to interpret biblical events related to biology.

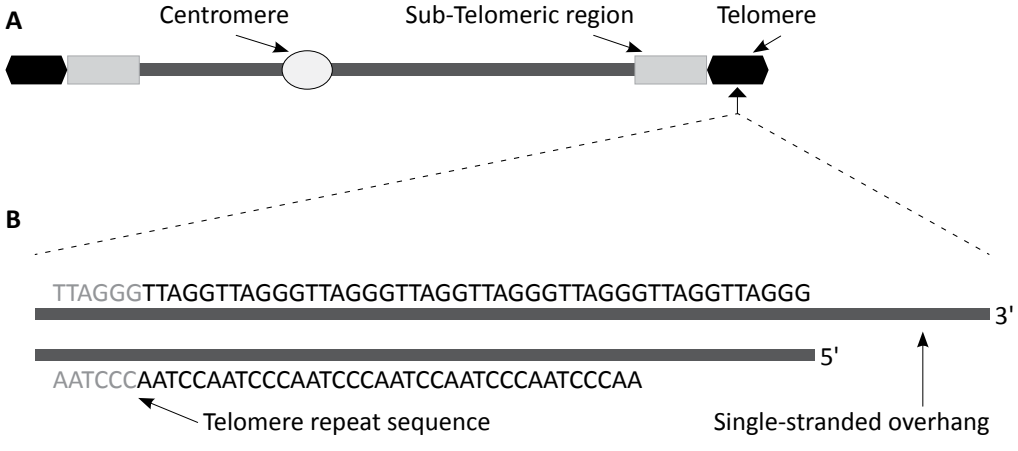

Figure 1. A. Chromosomal location of telomeres at the end points of two paired homologs. B. DNA sequence of the mammalian telomere repeat and an illustration of the single-stranded overhang used to form the D-loop.

* Terms marked with an asterisk are defined in the Glossary at the end of this article.

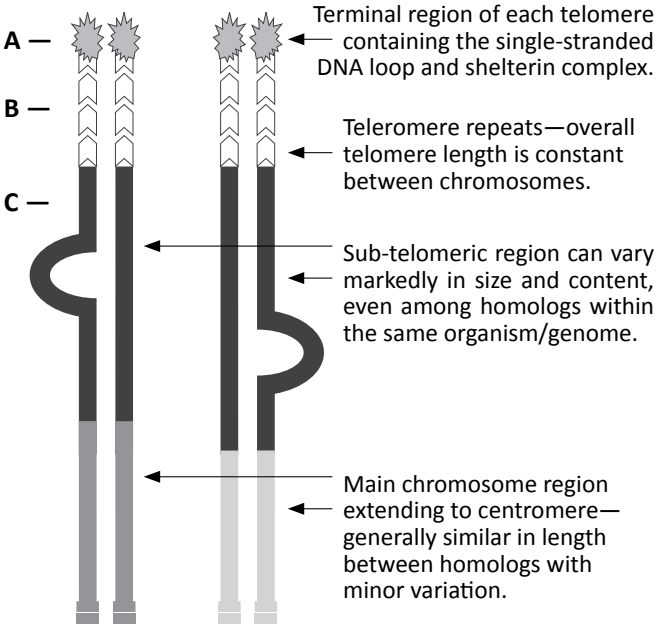

Figure 2. Two sets of aligned sister homologs showing the major components of the telomere: A) end-cap, B) telomere repeats, and C) subtelomere regions. Variability (length polymorphisms) of subtelomeres is depicted.

Telomere system structure and function

Telomere DNA structure

If the ends of linear eukaryotic chromosomes were unprotected, aberrant fusion to other chromosomes (via end-joining) and chromosome fragments (via homologous recombination) would make cell life impossible. Prokaryotes (eubacteria and archaea) typically have circular chromosomes, thus genome instability is less a concern. The telomere protective end-cap on linear chromosomes consists of a region of highly specific sequence repeats combined with a variety of telomere-specific proteins. The telomere is a very dynamic system that interacts with a variety of structures associated with the cell cycle, such as senescence, apoptosis, cancer/disease, stress responses, cellular differentiation, and overall organismal health and longevity. The slightest perturbance of the telomere DNA sequence, or any of the multiple proteins directly associated with the telomere, typically results in aberrant chromosome function during cell division, leading to cell senescence* and/or cell death called apoptosis*.[11,12]

The overall structure of the vertebrate telomere shown in figures 1 and 2 is representative of humans, all mammals, and most other vertebrate taxa. Figure 1 shows the telomere's three main features: A) the end-cap protein complex; B) the telomeric DNA repeats (also referred to as the telomere sequence); and C) the sub-telomeric DNA region—a distinctive and highly variable region directly adjacent to the telomere sequence that separates telomeres from the main chromosome.

The telomere DNA sequence at the chromosome terminus has been identified in a wide variety of eukaryotic organisms and is generally well-conserved, meaning it is very similar in all life forms, especially vertebrates.[13,14] Most telomere DNA sequences consists of a series of guanosine-rich tandem repeats that also forms a single-strand extension or overhang at the end of each chromosome (figure 1). The telomere repeat unit in mammals and most vertebrates consists of the six-nucleotide sequence TTAGGG (T_2AG_3) that is duplicated in tandem from a few hundred up to thousands of times.

Each human somatic cell* chromosome typically has 3,000–20,000 tandemly repeated TTAGGG telomere sequences at each end; other life forms have more or less, depending on the species.[15,16] One exception to this well-conserved homology is the ciliate protozoans, which use T_4G_4 or T_2G_4 sequences.[17] Although plant telomere biology has not been extensively studied, it appears that they also exhibit highly conserved repeats similar to higher animals with an extra T added at the beginning of the repeat, producing TTTAGGG (T_3AG_3).[18]

Telomere end caps are specialized DNA-protein complexes

The long string of highly conserved repeats provides a distinct motif that fosters the binding of a number of important proteins to facilitate the formation of the mature chromosome end-cap structure. Vertebrate telomere DNA is packaged by telomeric specific nucleosomes* and the HP1 binding protein (heterochromatin* protein 1) that shortens the number of telemetric repeats by about 40 base pairs compared to standard bulk nucleosomes in non-telomeric heterochromatin.[19] Thus, the telomere region is more compact and dense than other chromosomal regions, which adds to its protective capability. Telomere repeat binding proteins factors 1 and 2 (TRF1 and TRF2) bind directly to TTAGGG repeats.[20,21] These two proteins are the basal regulators of telomere length and interactive function. The TRF1 protein also binds to a variety of other proteins to form a protective telomeric structure consisting of six protein subunits called the shelterin complex (figure 3).

Proteins that bind to TRF1 include the TRF interacting factor 2 (TIN2), the TANK1 and TANK2 (tankyrase 1 and 2), the protector of telomeres protein 1 (POT1) and its associates, POT1 binding partner (TPP1) and the repressor-activator protein 1 (RAP1). The POT-TPP1 protein association forms a critical part of the shelterin complex and also binds to the single-stranded telomere G-tail.

The TRF2 protein facilitates TRF1 binding to the DNA through its interaction with TIN2 (figure 3). The TRF2 protein complex plays an important role in protecting single-strand DNA at the terminus. It also prevents aberrant break repair at the telomere by interacting with the cell's DNA damage response machinery.[20,22] Evidence of this role

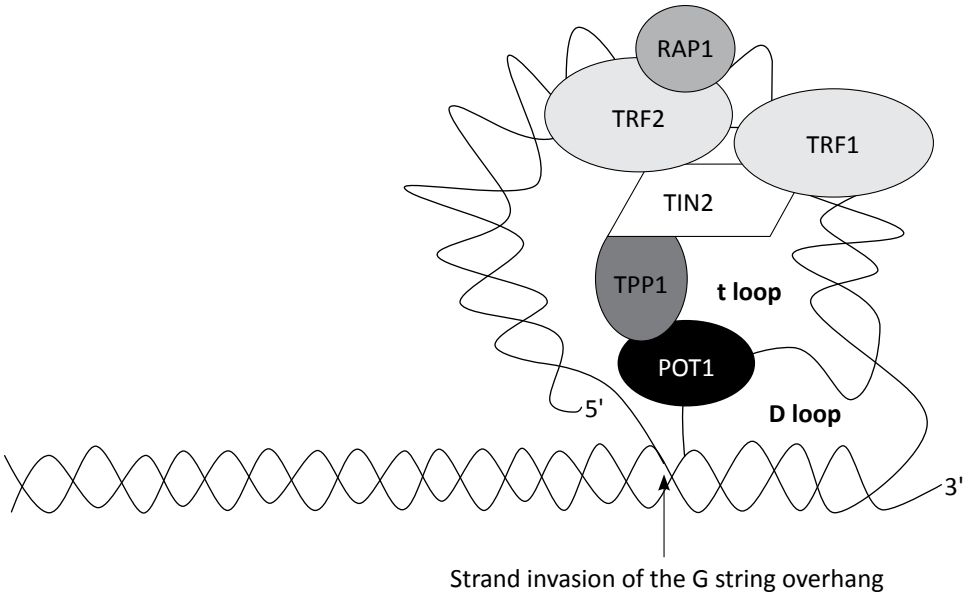

Figure 3. Telomeric double-stranded DNA in a complex with the six proteins comprising the shelterin complex; telomeric repeat binding factors (TRF1, TRF2, and RAP1), TERF1-interacting nuclear factors (TIN2, TPP1, and POT1). The TPP1-POT1 heterodimer regulates access of telomerase to it's telomeric DNA substrate. The single-stranded DNA overhang shown in Figure 1, is invading the double-stranded DNA region of the telomere to form the protective telomere (t)-loop. This creates a single-strand displacement (D)-loop at the site of invasion. Elements of the mammalian telomere complex also interact with other factors, many of which are associated with the DNA damage response mechanism. Putative interactions with cell signaling factors are also implicated, but not well understood at the time of this publication.

includes TRF2 mutations that are associated with a variety of cell pathologies related to chromosome instability.

The mature telomere end-cap DNA system forms a loopback structure.[13,23] The single-stranded G-tail telomere loop (the T-loop) folds back onto the telomere in the shelterin complex region (figure 3). The single-stranded G-tail anchors to the DNA-protein complex after invading the duplex DNA in openings called G-loops. The G-loop openings are specific sites in double-stranded DNA heterochromatin structures called G-quadruplexes designed to interact with single-stranded DNA. At the site where the G-tail invades the duplex DNA and base-pairs with the opposing strand, the G-strand at that site is displaced and forms a small loop termed the displacement loop or D-loop (figure 3). This DNA looping back mechanism is tightly integrated with the shelterin complex to form a strong chromosome terminus protective structure that regulates DNA damage response mechanisms.[22,24]

The two major signaling pathways involved in the mammalian cell DNA damage response are the ataxia telangiectasia mutated (ATM) kinase and ataxia Rad3-related (ATR) kinase signaling.[22–24] These pathways are critical for function, stability, and overall genome repair and maintenance. Both ATM and ATR are responsive to DNA damage at telomeres caused by progressive shortening or other structural aberrations.[16,25] If these pathways are not properly regulated, the linear chromosome end points would aberrantly repair, rendering cell life impossible. The regulation of DNA damage response pathways at telomeres is facilitated by the TRF2 and POT1 shelterin complex proteins which interact with the ATM and ATR pathways.[21,22]

Canadian telomere researcher and evolutionist Peter Lansdorp compared the DNA repair system vs the telomere maintenance paradox to the classic chicken-and-egg scenario.[25] The ubiquitous problem of 'what came first' is an overwhelming argument for irreducible complexity throughout the cell. If both complex systems were not simultaneously created in place, the eukaryotic cell would immediately self-destruct. In order for DNA damage control mechanisms and linear chromosomes to coexist in the same cell environment, both complete systems must have been simultaneously created. This is true for all of the thousands of components required for the cell's machinery.

Telomerase[26], the wonder protein

For life to perpetuate, some way must exist to rejuvenate telomeres in certain types of cells, especially stem and germ-line cells. This is accomplished by a ribonucleoprotein reverse transcriptase complex called *telomerase**.[11,19,27] Telomerase was first discovered in the protozoan parasite, *Tetrahymena*, by Carol Greider and Elizabeth Blackburn in 1985.[28] The core components of the complete telomerase complex consist of two telomerase reverse transcriptase (TERT) proteins forming a homodimer*, a telomerase RNA component (TERC), and the dyskerin protein complex.

In cells where TERT is expressed, telomerase is able to counteract telomere shortening by reverse transcribing the template section of its tightly integrated RNA component, the TERC.[27,31] Telomerase activity is partially or completely counterbalanced by the replication of the G-strand's complementary C-strand via the cell's standard DNA polymerase* replication machinery.[19,29] An exception to this rule is the fill-in operations in cancer cells that are delayed until the cell cycle's S-phase*. Then a novel non-Okazaki mechanism incrementally fills in the G-strand's complement.[30]

The TERT harbors the catalytic site for *de novo* synthesis of telomeric repeats from its integrated RNA molecule that contains a template for the TTAGGG repeats.[28,29,31] The TERT protein subunit is composed of three distinct domains,

1. the N-terminal extension containing RNA-interaction domains 1 and 2 labeled RID1 and RID2,
2. the reverse transcription domain where nucleotide transfer occurs, creating the DNA repeats on the G-strand, and
3. the C-terminal region for processing and recruitment to the telomere after it is translated. Mutations within the protein subunits of the telomerase ribonucleoprotein complex are associated with a wide variety of human diseases.

The RNA component of telomerase (TERC) contains a total of 451 nucleotides, forming an intricate secondary structure that integrates with the TERT and dyskerin protein subunits (figure 4).[31] One study that cloned and sequenced 32 TERC genes from diverse vertebrate taxa found that the overall sequence was highly conserved, indicating that the TERC secondary structure has an important role in the proper function of telomerase.[31]

Three primary functional sub-domains define the TERC RNA molecule (figure 4). One of these sub-domains contains the template region for telomere repeat synthesis. The telomere template itself (3'-CAAUCCCAAUC-5') occupies only 11 nucleotides, less than 3% of the total TERC sequence. The other two TERC domains (CR4/CR5 and ScaRNA) are involved in nuclear base recruitment. The TERC conformational structure forms an RNA scaffold for the various telomerase proteins to bind and integrate.

A third telomerase complex component, the major protein *dyskerin* along with other smaller subunits (NHP2, NOP10 and GAR1), occupies the 3' terminus of the TERC and functions to stabilize the entire ribonucleoprotein complex.[13,32] The irreducible complexity of the dyskerin protein is documented by the wide array of mutations in the dyskerin gene (DKC1) associated with a variety of diseases.[13,33] At present, 47 mutations and their disease

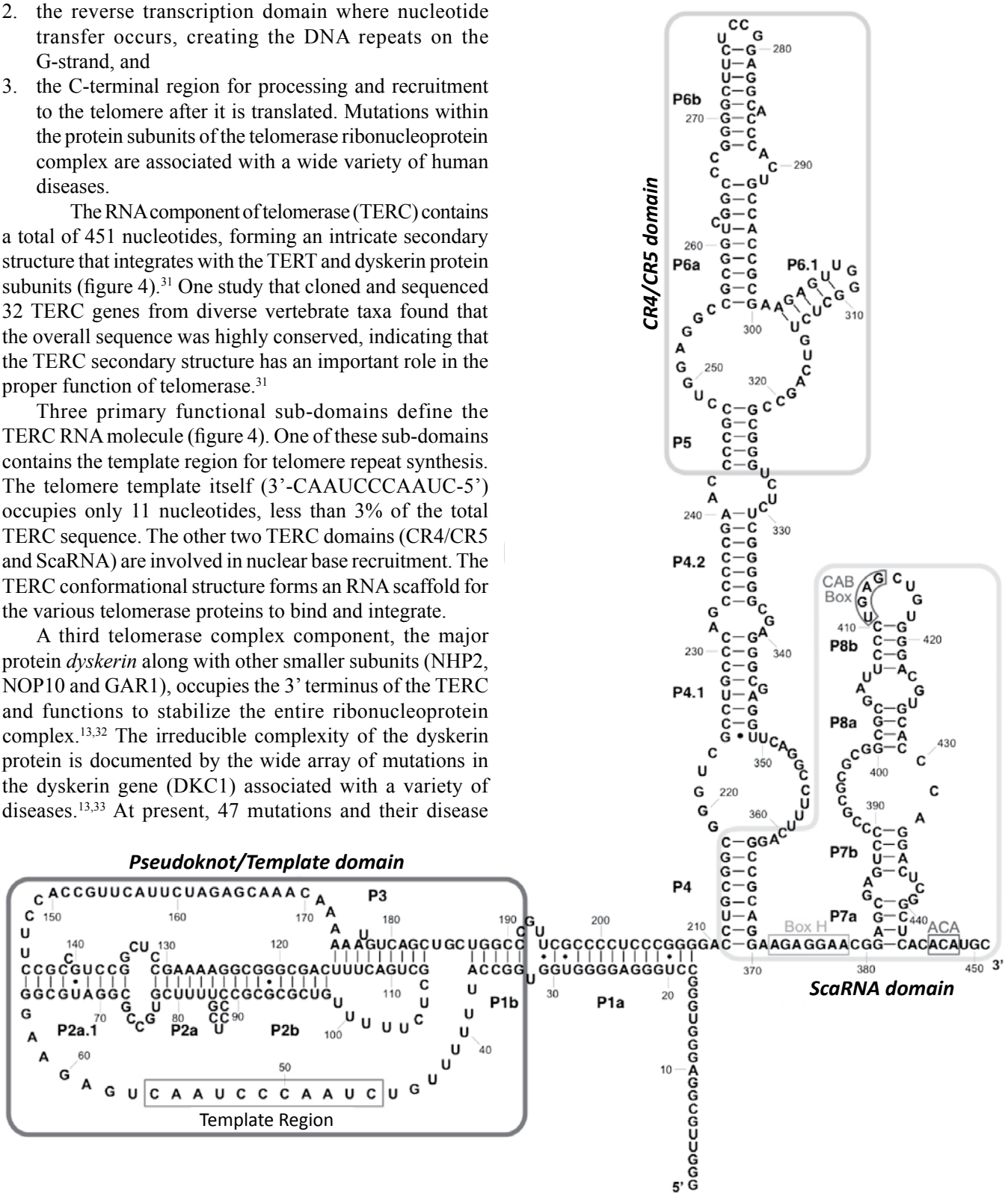

Figure 4. An illustration of the secondary structure of the RNA component of the human TERC which is 451 nucleotides. The three primary domains are depicted in addition to the telomere repeat template. This image is publicly available for viewing at the Telomerase Database (Chen *et al.*, ref. 31).

phenotypes in DKC1 have been characterized and listed in the telomerase database. As is true with many mutations in the other telomerase components, dyskerin mutations are associated with a wide range of physiological pathologies affecting the skin, bone, and circulatory system.[32,33]

Telomerase interacts with the shelterin components located at the terminal ends of the chromosome.[19] The POT1 protein that binds to the telomere DNA is an important DNA repair system suppressor that is critical in regulating telomerase activity.[22] The POT1 proteins complex with TPP1 proteins in the shelterin complex, functioning as a switch that regulates telomerase access to the telomere.[34] When access is allowed, the POT1-TPP1 complex switches roles from being a structural-protective component of the shelterin complex to an active processivity factor in telomerase elongation.[34] In the human cell system, telomere extension is enhanced by POT1-TPP1. This dramatic dual-purpose role for what appeared to be only a structural feature was completely unexpected.

The TERT telomerase component was also found to play a completely unanticipated and entirely different functional role as a transcriptional regulator of the Wnt signaling pathway, a process not known to be directly connected to telomere extension.[35] The Wnt signaling pathway controls the transcription of genes associated with cell proliferation, cell differentiation, and tumor progression.[36] This alternate role of TERT as a transcription factor, was discovered during a project focused on isolating regulatory proteins associated with Wnt signaling during embryo development.[35] The unexpected data came when TERT consistently co-precipitated with other DNA-binding proteins in association with a specific type of regulatory motif in DNA regions associated with genes in the Wnt signaling pathway.

Another surprise—telomeres are transcribed

Telomere structure and function research in recent years has provided a variety of examples that completely change the original idea of the chromosome terminus being a relatively static feature in the cell. Researchers originally envisioned a largely non-functional system for protecting linear chromosome ends and considered telomeres to be a fairly inactive genomic area. This view had some support because the histone* protein packaging system in DNA was even more compact in telomeres than in other heterochromatic areas of the genome.

One of the most surprising recent discoveries revealing new features of telomeres is the presence of large RNA molecules containing telomeric repeats,(called TERRA's) which have been identified in a variety of animals and fungi.[37] These TERRAs, which are actually transcribed from telomere repeats, form an integral part of telomeric heterochromatin structure. The TERRA discovery has opened up a whole new sub-field in telomere biology, further complicating our understanding of the complexity of telomeres.

The TERRAs appear to be transcribed in virtually all somatic mammalian cells via RNA polymerase II (RNAPII). Other polymerases (RNAPI and RNAPIII) are also suspected of transcribing TERRAs under some conditions.[37] The transcription of TERRAs actually begins in the sub-telomeric region, and then proceeds through the telomeric repeats in the centromere to telomere direction. The large TERRA transcripts contain a combination of both sub-telomeric and telomeric sequences, with the sub-telomeric region being the most variable between transcripts, indicating multiple transcription start sites and a variety of post-transcriptional processing options. Interestingly, TERRAs are also polyadenylated and contain the characteristic poly-A tails used in protein coding transcripts.

Once transcribed, TERRAs are thought to be integrated into the telomere structure, but in a transient manner to help regulate the telomere's functional state.[37] *Lower* TERRA levels have been associated with an *increase* in telomerase activity, supporting their possible role as a factor in dynamically silencing heterochromatin.[38] This helps explain why tumor progression that is associated with ectopic telomerase activity is accompanied by a reduction in TERRA levels.[39] Although TERRA regulation is currently poorly understood, researchers have determined that four protein factors associated with the non-sense mediated RNA decay (NMD) machinery are also active in regulating TERRAs.[40,41]

Epigenetic regulation of telomeres*

New research on epigenetic modification of mammalian telomeres has also opened up a whole new chapter in telomere biology.[5] Large non-coding RNAs have previously been implicated in epigenetic changes by their ability to recruit chromatin* re-modeling machinery to specific sites in the genome.[42] A recent discovery even implicates mixed-lineage leukemia (MLL) protein activity at telomeres.[43] The MLL proteins are well-known histone methyltransferases (histone modifying enzymes) involved in the positive regulation of various genes throughout the genome in addition to histone modification associated with epigenetic activity.[42]

Another important element of epigenetic regulation is DNA methylation. It is particularly important in the sub-telomere regions and, in vertebrates, is regulated by the three known major DNA methyltransferases.[38] The characteristic histone marks associated with silenced heterochromatin are also present. Thus, epigenetic factors also play an important role in the regulation of telomere structure and function in addition to affecting gene regulation in euchromatic areas.

In summary, an enormously complicated system involving epigenetic factors, TERRAs, shelterin proteins,

telomerase proteins and other connected cellular features are all involved in what we now define as a 'Telomere'. As research progresses, the telomere paradigm will undoubtedly get even more complicated. The activity surrounding the telomere also has profound implications for other connected cell processes such as DNA damage response mechanisms, cell-cycle controls, cell signaling, and nuclear structural integrity.

Telomeres in aging and disease

An inherent feature of somatic cells is that they periodically divide, requiring replication of their DNA. During chromosome replication, DNA polymerases are unable to completely replicate the lagging strand at the end of a chromosome, resulting in successively shorter telomere end sequences in each successive round of cell division. Because chromosomes systematically shorten with each round of cell division, the result is sometimes referred to as a 'mitotic clock'. This clock is not directly associated with elapsed time, but with the number of cell divisions that have elapsed.[5]

Telomere length eventually reaches a critical threshold point resulting in senescence (cell cycle arrest) and/or apoptosis (programmed cell death).[12,44] Vertebrate senescent cells are eventually eliminated by the innate immune system.[45] Senescent cells are also susceptible to an apoptosis cascade resulting in their elimination by self-phagocytosis*.[45] Once the telomeres have reached a critically short level that arrests the cell cycle, a built-in safeguard feature protects the cells from uncontrolled cell proliferation and tumor formation.[46]

Although somatic cells are periodically replaced by various stem cells that have fresh telomeres, a net overall loss in telomere length during the organism's lifespan occurs. The rate of telomeric sequence loss in the average human somatic cell is estimated to be between 15 and 40 nucleotides annually, and by age 80 they are about 60% shorter than at birth.[47] The total average lifetime loss of telomere length in human somatic cells is from 2,000 to 4,000 bases.[48,49]

In addition, physiological stresses such as obesity and smoking can increase lifetime telomere sequence loss up to 18%.[50] Psychological stress has also been shown to reduce telomerase activity, shorten telomeres, and as a result shorten lifespan.[51,52] Conversely, factors that improve the human physiology, such as vitamin intake (particularly antioxidants) were found to be highly correlated with telomere length increases.[53] Thus, telomeres are not only key indicators of cellular and organismal age, but their status also reflects nutrient intake and physical and psychological stresses.

The relationship between telomeres and organismal aging was originally discovered by analyzing patients with pathologies defined by rapid apparent 'aging' and classified under the general term 'progeria'. A progeroid pathological presentation typically exhibits a combination of symptoms including cataracts, grey hair, small stature, osteoporosis, nail atrophy, wrinkled skin, reduced reflexes and various cancers.[54,55] These progeroid conditions were often found to be associated with shortened telomeres, implicating a variety of genes that code for proteins involved in telomere function. Although still used in clinical settings, the term progeria is a somewhat ambiguous classification. Most disease conditions caused by telomere related mutations are now placed into one of three categories; *dyskeratosis congenita* (DKC), *aplastic anemia* (AA), and *idiopathic pulmonary fibrosis* (IPF). According to the telomerase database, 148 different mutations have now been identified and characterized. A majority of these have been found in the genes which encode the TERC, TERT, dyskerin and shelterin proteins at 40, 42, 44 and 18 total mutations, respectively.

Four different disease causing mutations have also been discovered in two genes that encode proteins which provide subunits for small nucleolar RNA-protein complexes (snoRNPs), nuclear based machines that aid in mRNA processing. Some progeroid type diseases are not directly related to a telomere component gene, but still affect telomere length. For example, one of the best documented and most severe progeria mutations affects a nuclear matrix protein (lamin A), causing the Hutchinson-Gilford Progeria Syndrome (HGPS), a disease characterized by extremely rapid aging and a median age of death at 13.[54] Mutations in this gene are not only associated with telomere length reductions but also with aberrations in both nuclear membrane permeability and overall nuclear matrix integrity.[55,56] Research has shown that the physiological causes of premature aging associated with telomeres are far more complex and interdependent than once thought.

Telomeres, cell longevity and systems biology

The role of telomeres as biological markers in cellular longevity was first highlighted in cell line cultures where differences were observed between normal somatic cells (having limited life-spans) and so-called immortal cells, including normal germ-line and cancer cells.[57,58] In the absence of telomerase activity, normal somatic cells progressively exhibit reduced telomere length with each cell cycle. In contrast, immortalized cell lines are characterized by lengthened telomeres and detectable telomerase activity. Understanding the factors that trigger and control aberrant telomerase production is critical in the study of cancers because the vast majority of human cancers display abnormal telomerase levels and lengthened telomeres.[57] Cancer cells do not usually contain *longer* telomeres compared to normal cells, but rather experience less telomere *loss*.[57] Telomerase expression has been found in close to 90% of all metastatic cancers, and thus is a significant cancer bio-marker.[20,57]

Shortly after a confirmed association between telomere length and cell longevity was made in the early 1990s, scientists also assumed that uncovering the master mechanism controlling human longevity was close at hand. Technological advances in laboratory automation and robotics have enabled the genome-wide study of gene activity. Researchers now had the ability to evaluate thousands of genes or proteins in a single experiment and determine which groups of genes were responsive to a given physiological event (e.g. cancer) or environmental cue. Typically, a targeted approach is used to focus on a particular organ or group of cells. Microarray* analysis of gene expression allowed researchers to determine which gene groups were up-regulated, down-regulated, or were completely unresponsive for a given set of conditions and/or tissues.

One of the first cell model systems to be exploited using new functional genomic technologies was the single-celled eukaryote *Saccharomyces cerevisiae* (baker's yeast). One study used 4,862 yeast strains in which one strain had each open reading frame (ORF) replaced with a construct containing an antibiotic marker, systematically knocking out each gene in the genome while also providing antibiotic resistance for selection.[59] This provided a knockout phenotype for almost 90% of the yeast genome's 5,538 genes so that associations between cell processes and specific genes could be made. By using this system, researchers discovered 150 genes associated with altered telomere length.[59] Gene classes implicated in controlling telomere length included DNA/RNA metabolism, chromatin modification, and vacuolar traffic. In a follow-up study, Gatbonton *et al.* used a similar approach and identified an additional 88 genes associated with telomere length, bringing the total number of genes affecting telomere length to over 238.[60] The gene-network picture of telomere length and aging had now become enormously more complicated, illustrating a level of complexity unimagined a few years ago.[61–64]

Difficulties for telomere evolution

The telomere system is highly conserved across almost all multicellular organisms

The vertebrate telomeric repeat sequence represented by the RNA component of telomerase (TERC) is very similar across diverse taxa and therefore does not provide robust data to develop phylogenies. Evolutionary (mutational) change is thought to be constrained because the sequence is preserved due to the highly specific binding required for a wide variety of proteins with conserved motifs.[14] Evolutionary models require the TERC genes, along with all of the proteins in both the shelterin and telomerase enzyme complexes, to have evolved by random mutations in concert so as to maintain complete functional interdependence. High sequence homology (conservation), rather than providing progressively dissimilar strings for alignment and parsimony, argues against evolutionary interpretations of the data. The complex telomere system appears suddenly in eukaryotes and then remains largely static.

The evolutionary origin of telomeres is so difficult to explain that noticeably few scientists are even willing to tackle this problem. Furthermore, all of the models postulated to explain telomere evolution are highly ambiguous and generalized. Noting the paucity of attention devoted to the topic combined with the extensive research completed in telomere biology, Fajkus *et al.* wrote, "one area, that of the response of telomeres to evolutionary change, has failed to be addressed in detail." They then attempted to describe telomere evolution primarily within the context of plants where minor variations within the repeat telomere structure has been found.[18] They proposed a hypothetical and highly ambiguous model where "aberrant activity" of mutant telomere proteins at the protein cap could lead to chromosome fusions and new karyotypes.

The Fajkus *et al.* model postulates that co-evolution of telomere proteins and telomere repeats first occurred by a mutation in a cap protein that disrupted the telomere's protection system. As a result, aberrant fusions occurred, causing new karyotypes and novel telomere repeat sequences. This seems to be a repeating theme in the field of genome evolution where complete disruption and chaos is somehow initiated in an otherwise complex and stable system which then magically spits out some new successful variant. Not only does this line of reasoning fail to account for how the complex interdependent system in question got there in the first place, but it does not take into account the catastrophic failure that occurs when irreducibly complex systems lose one or more key components. While plant biological systems tend to be more plastic and resilient to genomic aberrations than vertebrate animals, key genome stabilizing features like telomeres, tolerate very little disruption.[65]

Drosophila: an intermediate telomere system?

Evolutionary biologists have also focused on insects as a source for possible mechanisms for telomere evolution, notably the system in the *Drosophila melanogaster* (fruit fly) genome and several other insect taxa. *Drosophila* are unusual in that they use tandem arrays of retrotransposons (virus-like sequences)* to create the telomere repeat structure.[66,67] The three retrotransposons in *Drosophila* telomeres (collectively abbreviated as HTT elements), all of which have long untranslated regions (UTRs), comprise half the entire element.[66,67] The entire element exhibits a sequence bias very similar to the standard telomere repeats used in other eukaryotes. The sequence is so similar to the standard telomere repeats in animals that these elements are also able to form G-quadruplex structures important for

end-cap formation. The telomeres are elongated by both a targeted transposition of these elements and homologous recombination between the elements.[66,67]

From an evolutionary perspective, the presence/absence of telomerase does not follow any sort of logical line of descent. Furthermore, the transposable element* system is about as interdependent and complicated as systems that also employ telomerase. Thus, the telomere system in *Drosophila*, while worthy of further study, does not appear to offer any answers supporting telomere evolution.

Complicating matters even more is the diversity of the retroelement* telomere sequence within a species. The single species *Drosophila melanogaster* alone has a range of 68 to 99% nucleotide identity within just the HeTA-A element class, one of the three major retroelement classes forming *Drosophila* telomeric repeats.[67,69] And for the encoded proteins, the amino-acid sequences are 76 to 100% identical.

These are very broad numbers for a single species, and thus any attempt to construct accurate alignments and predictive phylogenies among diverse taxa would be extremely problematic. Although much sequence diversity exists for retroelement-based telomeres, even within a species, strong sequence conservation exists for the canonical regions that provide the key motifs for DNA binding proteins.[68,69] This results in a paradox: extreme sequence conservation prohibits the use of TERC-based telomere sequences for phylogenetics* while sequence diversity prohibits the use of retroelement-based telomere sequences.

Did telomeres originally evolve in cells?

Evolutionists speculate that early hypothetical eukaryotes formed a nucleus replete with linear chromosomes shortly after they absorbed a circular prokaryotic genome as a result of endosymbiosis*, an easily discredited evolutionary model.[71] This unlikely hypothetical scenario assumes telomeres originated from the non-homologous recombination of retroviral elements following a circular genome fragmentation event in which it was necessary for the cell to protect the exposed ends of its chromosomal fragments. The unusual *Drosophila* retroelement telomere system described previously is thought to support this scenario.[72]

One of many major difficulties with this model is: how were chromosome ends protected until this system evolved? The *Drosophila* system involves the same integration with the cell's DNA repair mechanisms, cell cycle pathways, epigenetic mechanisms, and protein end-cap structures as do other eukaryotic systems that utilize telomerase. In fact, it is widely recognized that the *Drosophila* system is functionally similar and as complex as other systems that use telomerase.[66]

Because the telomere system is ubiquitous in all eukaryote systems so-far studied, it is speculated that it must have evolved very early, shortly after the first endosymbiotic event. However, no evidence for any intermediate system between circular chromosomes and linear eukaryotic chromosomes exists. Another problem is that the evolution of a complex telomere system would have contained many useless and non-selectable intermediate components prior to achieving an integrated and functional system. Because the telomere system is enormously complex, parsimony difficulties arise when taking into account large groups of the major protein sequences involved. Extremely high similarity for some telomere components also confounds theories of convergent evolution.

Some evolutionists argue that many mutations in the telomere system do not affect an individual's health until after reproductive age, allowing for mutational activity to be carried along throughout a number of generations and giving enough time for a new telomere system to evolve.[73] However, given the documented severe adverse effects of nearly all telomere-related mutations so far characterized, it is highly doubtful that multiple telomere mutations could be carried by an organism without causing severe disease.

The complex mixture of interrelated parts of the telomere system that must function as a complete set argues against microbes-to-man evolution. As documented by the numerous mutations causing pathologies listed in the Telomere Database, when any one of the various individual components of the system is perturbed, the life or health of the entire organism is typically at risk. In most cases, any type of a telomere-based mutation will confer a decrease in organismal fitness and a shorter reproductive life span. Irreducibly complex systems involving telomeres cannot be made to fit neo-Darwinian evolution.[74]

*The sub-telomere segment**

One telomere-related region that has drawn the attention of evolutionary biologists is located in the sub-telomere segment (see figures 1 and 2). In addition to the telomere repeats at the chromosome end, the sub-telomere DNA region that separates the telomere repeats from the rest of the chromosome is very distinctive in its structural make-up. This complex mosaic region contains a variety of low-copy repeats, segmental duplications, possible degenerate telomeric repeats, and a wide variety of genes.[14]

Some of the sub-telomere gene classes encode tubulins*, transcription factors*, olfactory receptors*, and cytokine receptors*. Many of these genes occur in families within the sub-telomere. One interesting feature of sub-telomeres is the size and variability of the polymorphisms that have been documented between homologs. Length polymorphisms of up to 260 kilobases long have been documented in humans.[14,75] These polymorphisms not only vary in length and sequence content between and within species, but

also between sister homologs in the same genome. Yet another interesting feature of the sub-telomere region is an exceptionally high rate of meiotic recombination important to the rest of the genome.[75,76]

Because the sub-telomere region is variable in length, gene rich, contains gene duplications, and is subject to high levels of meiotic exchange, it has caught the attention of some biologists as a potential mechanistic hot spot for genome evolution. Current models of molecular evolution rely on gene duplication and subsequent recombination as a key mechanism. However, the model of gene or genome fragment duplication as a viable process to fuel Darwinian evolution is untenable for reasons beyond the scope of this review. For a creationist interpretation and review see Truman and Heisig,[77] Bergman,[78] Liu and Moran,[79] Liu,[80] and Lightner.[81]

The sub-telomere regions of various genomes are an important area of study from a creationist perspective because these genome segments appear to contain highly designed dynamic features. The molecular mechanisms operating in sub-telomeres could be related to genetic diversity, providing molecular models associated with historical events such as the post-Flood diversification of created kinds (baramins).

Contiguous DNA sequence spanning these regions has been hampered by a lack of gap closure due to current limitations in DNA sequencing technology and computational assembly. Another limiting factor is the high level of polymorphism combined with the extreme variation in segment length between not only individuals, but sister chromosome homologs in the same diploid genome. Nevertheless, research in this area utilizing publicly available nucleotide and protein sequence data could be a very fruitful endeavor for creation-based scientists wanting to understand built-in mechanisms of adaptation.

Conclusions

The protection of the linear chromosome terminus involves highly specific DNA conformations of both double- and single-stranded DNA complexes, RNAs, and a variety of specifically designed proteins. Some of these proteins are tailored to binding double-stranded DNA and others are engineered for binding single-stranded DNA. Based on studies that evaluate mutations in the genes that encode the shelterin proteins and telomeric sequence, little deviation from the conserved sequence is tolerated, indicating that the overall structure of telomeres is tightly engineered.

This intricate chromosomal cap structure provided by the shelterin complex prevents cellular DNA-damage response machinery from performing end-repair operations that would result in aberrant chromosomal fusions throughout the genome. If allowed to proceed, this catastrophic activity would immediately arrest the cell cycle, making biological life impossible.

Extreme sequence conservation is a two-edged sword for the evolutionary paradigm. While high sequence similarity enables highly alignable comparisons across diverse taxa, supposedly tying them together in a molecular evolutionary sense, it also destroys the argument because no evidence exists for gradual transitions from a progenitor sequence. Furthermore, these highly conserved genes/proteins always represent machinery required for fundamental biological processes where sequence conservation is required and no other intermediate conformational structure would be functional.

In other words, the design tolerances are very tight. Although the entire cellular apparatus surrounding the maintenance and function of telomeres is incredibly complex, it is also similar across taxa and linear chromosome endpoints represent similar DNA design requirements. The supposed evolutionary transition from small, circular, non-nucleated, non-repetitive prokaryotic genomes to large complex eukaryotic genomes is a critical hurdle for the evolutionary paradigm to overcome and the dynamics of linear chromosome endpoints is just one of many confounding issues.

Glossary

Apoptosis is the process of programmed cell death (PCD) that occurs in multicellular organisms in which the cell uses specialized cellular machinery to systematically shut itself down and recycle its components. Cell suicide is also used to control cell number and eliminate certain cells such as those between the fingers in the developing human embryo.

Chromatin is the combination of DNA, histones, and other proteins that are designed to package DNA inside the nuclei of eukaryotic cells. Chromatin is divided between heterochromatin (condensed) and euchromatin (extended) forms.

Cytokine receptors are cell receptors that bind locally acting hormone-like structures called cytokines. A deficiency of cytokine receptors has been directly linked to certain immunodeficiency diseases.

Endosymbiosis is a theory postulated to explain the origins of mitochondria and plastids (chloroplasts), organelles in eukaryotic cells. The theory hypothesizes that these organelles first originated as separate prokaryotic organisms taken inside the primitive prokaryotic cell as endosymbionts.

Epigenetics refers to chemical modifications in DNA other than changes in the actual DNA sequence. Examples include chemical factors, such as the attachment of methyl molecules and the acetylation of histone proteins used to regulate the organism's genome. Highly methylated areas of the geome are often less genetically active.

Heterochromatin is highly packaged DNA, which makes it less accessible to protein factors that bind DNA. Its function includes gene regulation and the protection of chromosome integrity.

Histones are alkaline protein spools around which DNA winds to package and assemble the DNA into structural units called nucleosomes. They are the major protein components of chromatin, and play a role in gene regulation.

Homodimer is a protein complex constructed of two polypeptides that are identical in their amino acids.

Microarray technology, for the purpose of studying gene expression, typically involves thousands of short sections of specific single-stranded DNA sequences (representing genes) immobilized on a glass slide or other substrate, referred to as the probe. Messenger RNA transcripts are then isolated from a target tissue of interest, converted to complementary DNAs, amplified, fluorescently labeled and then hybridized to the probe. After the excess DNA is washed away, complementary hybridization of probe and target DNA is determined by laser-based fluorescence detection. For detection of up and down regulated genes, two sets of RNA from the same tissue subjected to different growth/stimuli conditions, are labeled in different colors and mixed prior to hybridization.

Nucleosome is a repeating set of chromatin subunits in eukaryotic cells consisting of DNA coiled around a core of protein histones that are shaped like thread spools. The nucleosome allows the DNA to be packed in an orderly way, yet also allows for rapid unwinding so that mRNA can be made when needed to produce protein for the cell.

Olfactory receptors positioned in the membranes of olfactory neurons are specialized proteins responsible for the detection of odor molecules.

Self phagocytosis is the process by which a cell systematically dismantles itself and recycles the chemical components for safe elimination or reuse in other cells. It is the final phase of apoptosis.

Phylogenetics is the study of the supposed common ancestry relationships of various organisms. The computational use of molecular comparative sequence data (nucleotide and protein) is common.

Polymerases are large specialized (enzyme) protein complexes whose primary function is to produce polymers of nucleic acids including mRNA and DNA.

Progeria is general diagnosis for a class of genetic disorders characterized by the appearance of accelerated aging and various degenerative pathologies. Progeria comes from the Greek word *progeros*, meaning 'prematurely old'.

Retroelements are virus-like DNA segments in the genome that contain a reverse transcriptase gene. They can transpose via an RNA intermediate by a process called retrotransposition.

Cell senescence is the process by which a cell loses the ability to divide and shuts down many of its normal activities and, in many cases, is then removed by the immune system.

Somatic cells are those which form the body of an organism as opposed to germ line (sperm and egg cells).

S-phase is the stage in cell division in which the cell duplicates its DNA by semi-conservative replication.

Teleological argument is based on evidence of order, purpose, and design in the natural world. The term 'teleological' is derived from the Greek *telos*, meaning "end" or "purpose".

Transcription factors are proteins that bind to specific DNA sequences to regulate the transcription of genetic information from DNA to mRNA.

Transposable elements (also called transposons) are sequences of DNA that can move or (transpose) to new positions within the genome.

Tubulins are proteins such as α-tubulin and β-tubulin that are used to make microtubules in the cell, one of the most important rod-like skeletal and structural components in the cell.

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