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Minireview

Alternatives to telomerase: keeping linear chromosomes via telomeric circles

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Abstract Recombination is often capable of lengthening telomeres in situations where telomerase is absent. This recombinational telomere maintenance is often accompanied by telomeric instability including the accumulation of extrachromosomal telomeric circles (t-circles). Recent results of in vivo and in vitro experiments have suggested that t-circles can lead to the production of extended stretches of telomeric DNA by serving as templates for rolling-circle synthesis. This implies that t-circles can provide an efficient means of telomere elongation. The existence of t-circles in both nuclear and mitochondrial compartments of distantly related species suggests that they may be important contributors to an evolutionary conserved telomerase-independent mechanism of maintenance of telomeric tandem arrays.

Keywords: Telomere; T-circle; Rolling-circle; Mitochondrial DNA; Recombination; Alternative lengthening of telomere

1. Recombination as an alternative to telomerase

Telomeres, the DNA–protein complexes at the ends of linear DNA molecules, protect DNA from degradation and fusion. Because of the end-replication problem [1,2], chromosomes lose bases from their termini with each cell division. The most widely known solution to this problem is provided by telomerase, which adds de novo telomeric repeats onto chromosomal termini [3,4]. However, telomerase is not the only mechanism of telomere maintenance. *Drosophila*, for example, utilizes two families of retrotransposons as its telomeres [5]. In addition, certain bacterial chromosomes [6], plastid genomes [7] and mitochondrial DNAs (mtDNA) [8] terminate their telomeres in covalently closed loops that allow the synthesis of linear DNA via Cavalier-Smith–Bateman replication scheme [9,10]. Of the known telomerase-independent mechanisms of telomere maintenance, perhaps the most important involves homologous recombination [11,12].

Recombinational telomere elongation (RTE) appears to be responsible for telomere maintenance in a diverse assortment of situations. One of the major clinical importances involves a subset of human cancers. Most human somatic cells have low or no telomerase activity and, as a consequence, have a limited replicative capacity. In contrast, the vast majority of human tumor cells are immortal due to an active telomere maintenance pathway. Although telomerase appears responsible for telomere maintenance in most cases, ~5–10% of human cancers have no detectable telomerase [13] and appear to maintain telomeres using alternative lengthening of telomeres (ALT) [12]. ALT tumors and cell lines have telomeres that are highly heterogeneous in length, ranging from abnormally short (<1 kb) to abnormally long (>20 kb). They are also characterized by the presence of ALT-associated PML (promyelocytic leukemia) bodies (APBs). These intracellular complexes contain telomeric DNA, telomere binding proteins, and proteins known to function in recombination [14]. Strong evidence that telomere maintenance in ALT cells is recombinational comes from an experiment that showed that a sequence tag initially present in one telomere in an ALT cell line commonly got spread to additional telomeres [15].

RTE is best understood in yeast where it readily occurs in cells mutated to lack telomerase. It has been observed in at least four yeast species but most studied in *Saccharomyces cerevisiae* and *Kluyveromyces lactis*. Deletion of telomerase leads to gradual telomere shortening over 50–100 cell divisions normally accompanied by a growth senescence. While most cells do not survive beyond the peak of senescence, those that do (survivors) emerge with telomeres lengthened by recombination, as indicated by their dependence upon *RAD52*. In *S. cerevisiae*, the unusual arrangement at chromosome ends, with telomeric repeat arrays often separated by 6–7 kb Y′ elements, leads to the appearance of two types of survivors. Type I survivors maintain relatively short telomeres but have amplified arrays of the subtelomeric Y′ element [16]. Type II survivors lack the Y′ amplification but instead have lengthened terminal arrays of telomeric repeats [17]. In *K. lactis*, where

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Abbreviations: ALT, alternative lengthening of telomeres; APB, ALT associated PML bodies; ATM, ataxia-telangiectasia mutated; bp, base pair; EM, electron microscopy; mtDNA, mitochondrial DNA; nt, nucleotide; PML bodies, promyelocytic leukemia bodies; RTE, recombinational telomere elongation; spcDNA, small polydispersed cirular DNA; t-circles, telomeric circles; t-loop, telomeric loop; TRAP, telomere repeat amplification protocol; TRD, telomeric rapid deletion

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telomeric repeat arrays are confined to the very termini of chromosomes, survivors are only of the Type II variety [18].

Recombination has also been proposed to be responsible for telomere maintenance in several situations where telomerase is naturally absent. These include the chromosomal telomeres of the dipteran insects *Chironomous* and *Anopheles* [19,20], as well as those from certain plants [21]. In each of these cases, canonical short telomeric repeats of the sort synthesized by telomerase are missing at chromosome ends and appear replaced by larger, more complex repetitive elements. Other likely natural examples of RTE include the linear DNA molecules from mitochondria of certain ciliated protozoans and yeasts that terminate with tandem arrays of repeats, tens to hundreds of base pairs (bps) in length [22,23].

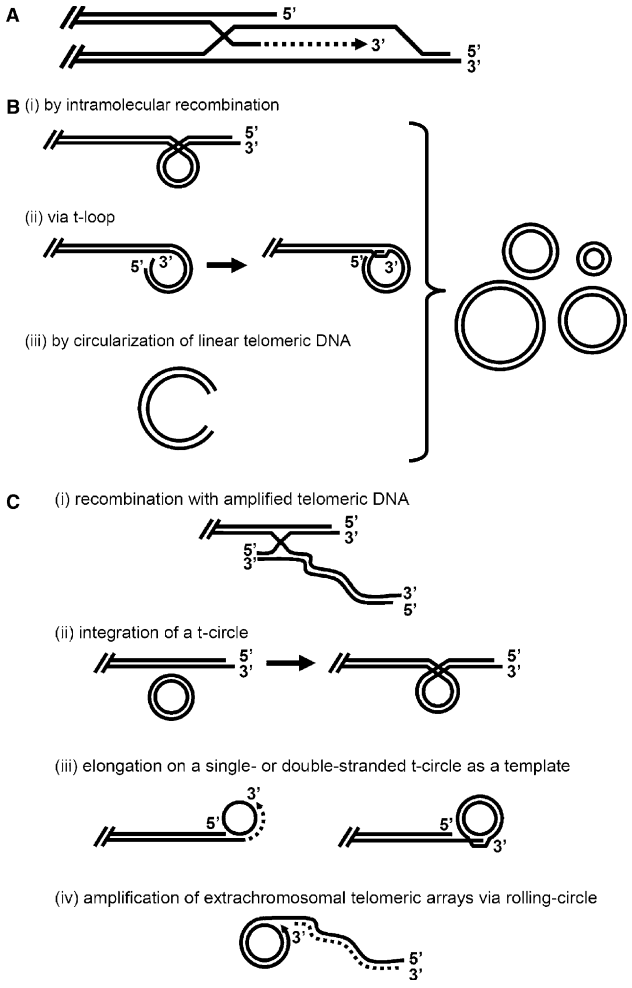

Fig. 1. Possible roles of t-circles in RTE. (A) T-circle-independent RTE. The 3′ telomeric overhang of one telomere may invade the double-stranded region of another telomere and use its complementary strand as a template. (B) Possible mechanisms for t-circle formation. (i) Homologous intramolecular recombination between telomeric repeats; (ii) homologous intramolecular recombination initiated at a t-loop; (iii) ligation of linear telomeric fragments. (C) Possible mechanisms of RTE mediated by extrachromosomal telomeric DNA. (i) Recombination with a linear telomeric fragment; (ii) recombination with a t-circle; (iii) extension of a telomeric end by rolling-circle synthesis using a t-circle as template; (iv) amplification of extrachromosomal telomeric arrays mediated by rolling-circle replication of t-circles. Recombination of these extrachromosomal arrays with chromosome ends could then produce telomere elongation.

The mechanisms by which RTE occurs are poorly understood and may turn out to be diverse. A commonly suggested mechanism proposes that the terminal 3′ overhang from one telomere strand invades another telomere and has its 3′ end extended by a DNA polymerase (Fig. 1A). In this way, the invading telomere might become longer than any telomere previously present in the cell. Although recombination between telomeres is likely to be a major mechanism for RTE, accumulating evidence suggests that one class of extrachromosomal telomeric DNA, namely telomeric circles (t-circles), might often play a special role in the process. Table 1 lists published examples of extrachromosomal telomeric DNA.

2. Linear mitochondrial genomes: t-circles in a natural telomerase-deficient system

Although human mtDNA is represented by a covalently closed circle, mitochondria of fungal and plant species harbor mostly linear concatemers of the genome equivalent with only a small proportion of circular molecules and branched structures (reviewed in [24,25]). However, a number of species contain linear mtDNA molecules of defined lengths terminating with specific structures termed mitochondrial telomeres. These genomes occur randomly scattered in phylogenetically distant taxa such as protozoans, algae, yeasts, oomycete fungi, molds and even several lower metazoan species, suggesting that linear mitochondrial genomes evolved more than once [26]. In several cases, data indicate that these linear genomes employ an active telomere maintenance mechanism that provides a solution to the end-replication problem and allows perpetuation of the linear form in subsequent cell division cycles. Since no counterpart of telomerase was detected in mitochondria, maintenance of their telomeres likely involves alternative replication strategies [27]. Morin and Cech [28] proposed that the tandem repetitions of 31–53 bp units found at the ends of the linear mtDNA in several *Tetrahymena* species are maintained by inter-telomeric recombination.

Mitochondrial telomeres in the yeast species, *Candida parapsilosis*, *C. salmanticensis* and *Pichia philodendri*, have similar organization as those in *Tetrahymena* [23] implying an analogous mechanism of their replication. However, recent data favor another possible mechanism. Investigation of mtDNA employing two-dimensional (2D) agarose gel electrophoresis and electron microscopy (EM) demonstrated the presence of minicircular DNA molecules derived exclusively from the telomeric sequence [29]. Mitochondrial t-circles are present as series of integral multiples of tandem repeat units consistent with being involved in the telomere dynamics. Importantly, screening of isolates from three genetically distinct groups of *C. parapsilosis* uncovered several strains with alteration in the molecular architecture of their mtDNA. Mitochondria of these strains lack t-circles and contain genomes with circular maps formed by fusion of termini and accompanied by deletions of the telomeric sequences. The occurrence of t-circles correlated with the presence of the linear form argues that they are associated with a recombinational mode of the telomere elongation [30]. An active role of t-circles in the telomere maintenance was suggested by recent results of 2D gel electrophoresis and EM analysis, which demonstrated that the mitochondrial t-circles generate rolling-circle intermediates (L.

Table 1
Known examples of extrachromosomal telomeric DNA

Organism	Nature of the extrachromosomal telomeric DNA	References
Yeasts		
Saccharomyces cerevisiae	Circles with telomeric and Y′ elements	[38,39]
Kluyveromyces lactis	Extrachromosomal telomeric DNAs in long telomere mutants	[36]
Insects		
Chironomus	>20 kb, RNA–DNA complexes	[54]
Plants		
Wheat	Extrachromosomal telomeric fragments	[55]
Amphibians		
Xenopus laevis	Telomeric extrachromosomal circular DNA (tel-eccDNA)	[48]
Mammals		
Rodent and human cell lines	Telomeric small polydispersed circular DNA (tel-spcDNA)	[14,46,47]
Human telomerase-negative cell lines	Linear extrachromosomal telomeric fragments	[43,44]
$Atm^{-/-}$ cells (telomerase-positive)	Extrachromosomal telomeric DNA	[45]
Yeast mitochondria		
Candida parapsilosis, *Candida salmanticensis*, *Pichia philodendri*	Extragenomic telomeric minicircles in species with linear mitochondrial genome	[29]

Tomaska, A.M. Makhov, J.D. Griffith and J. Nosek, unpublished data). Such a mechanism could result in long tandem arrays of the telomeric sequence that may recombine with the linear mtDNA molecules to lengthen the termini.

3. T-circles can promote RTE in *K. lactis*

Telomeric elongation caused by t-circles was extensively studied in *K. lactis*. Telomerase deletion mutants of *K. lactis* produce post-senescence survivors with elongated telomere repeat tracts using recombination [18]. By using cells containing two types of telomeric repeats, it was shown that recombinational telomere elongation generated repeating patterns common in most or all telomeres of survivors retaining both repeat types [31]. This pattern was consistent with the possibility that telomere elongation had occurred from a very small (~100 bp) t-circle being used as a template for rolling-circle replication. The commonality of pattern between telomeres within a given survivor (but not between different survivors) suggested that once a single long telomere had been generated in a cell, its sequence could then be readily spread to most or all other telomeres in the cell through inter-telomeric gene conversion. This idea was termed the Roll and Spread Model.

Additional evidence that spreading of sequence from one telomere to multiple telomeres occurs in telomerase deletion mutants of *K. lactis* has come from studies using strains containing a *URA3* gene inserted close to a single telomere [32]. Gene conversion between homologous subtelomeric sequences was shown to be enormously elevated in a telomerase deletion mutant and could readily result in spreading *URA3* to most or all other telomeres in the cell. More recent work has confirmed that telomeric repeats can spread from one telomere to all other telomeres during the formation of post-senescence survivors (Z. Topcu and M. McEachern, unpublished data).

Direct evidence that t-circles can bring about elongation of telomeres in *K. lactis* has come from transformation experiments [31]. 1.6 kb circles of DNA containing a cloned *K. lactis* telomere and a *URA3* gene were constructed in vitro. Ura^+ transformants of wild-type *K. lactis* cells were typically found to have a single telomere extended by the addition of many tandem copies of the 1.6 kb sequence. Tandem arrays were not produced when a similar telomere-*URA3* sequence was transformed in linear form. Transformation of the 1.6 kb circle into telomerase deletion cells produced tandem arrays of the telomere-*URA3* sequence at multiple telomeres. Experiments done by mixing two forms of the circle differing at a single restriction site demonstrated that all integrated copies of the 1.6 kb sequences were derived from a single molecule.

More recent experiments have shown that a mostly single-stranded 100 nucleotide (nt) t-circle (a size consistent with the repeating patterns described above) can also promote RTE in *K. lactis* [33]. Because the t-circles carry no selectable marker, detection of sequence derived from these tiny circles was carried out by co-transformation with a replicating plasmid and by subsequent screening of telomeres of the transformants for the presence of a sequence tag present on the 100 nt circle. ~1% of transformants were found to have incorporated sequence from the circle. The tandem arrays derived from the 100 nt circles were much shorter than those produced by the 1.6 kb circle and appeared to be of sizes (hundreds of bps) consistent with the extent of telomere elongation seen in *K. lactis* telomerase deletion cells. Interestingly, t-circles constructed of either strand of the telomere were each capable of leading to telomere elongation. Evidence from other laboratories has shown that DNA circles just tens of nucleotides in size, including those composed of human telomeric repeats, can be used by DNA polymerases in vitro for rolling-circle synthesis [34,35].

A key prediction of the Roll and Spread Model is that *K. lactis* cells must, at least at low frequency, be capable of generating tiny t-circles. While such circles are yet to be observed in a telomerase deletion mutant, they have been detected in certain mutants with highly elongated telomeres. Such mutants produce an abundant amount of extrachromosomal telomeric DNA, much of which often migrates in front of a 500 bp marker fragment [36]. Examination of this material in 2D gels and by EM has revealed that it is mostly composed of single stranded and double stranded circles (C. Groff-Vindman, S.

Natarajan, S. Iyer, A. Cesare, J. Griffith, and M. McEachern, unpublished data). Thus, although proof that t-circles are used to elongate telomeres in *K. lactis* post-senescence survivors remains lacking, considerable evidence favors that possibility.

Based on the abrupt appearance of post-senescence survivors, small t-circles have also been postulated to be responsible for the Type II survivors seen in *S. cerevisiae* [37]. Conceivably, circles composed of telomeric repeats and subtelomeric Y′ elements could play a role in the generation of Type I survivors. Such circles are known to occur in wild-type *S. cerevisiae* strains where they can excise from and integrate into DNA near telomeres at appreciable frequencies [38,39]. Formation of Type I and Type II survivors in *S. cerevisiae* depends upon different recombination genes [37,40]. This may suggest that the mechanisms of their formation are very different. Alternatively, different recombinational pathways may be needed to bring about recombination with large Y′ circles and with small t-circles of heterogeneous sequence as suggested by some recent data [41].

4. Extrachromosomal telomeric DNA in vertebrates

It has become clear in recent years that at least some vertebrate cells generate abundant extrachromosomal telomeric DNAs including t-circles. Recombination between telomeric sequences in human ALT cells leads to dramatic lengthening of telomeres as well as telomeric instability [12]. Manifestations of this instability include the occurrence of telomeric deletions that may be similar to the telomere rapid deletion (TRD) of yeast [42]. The ALT phenotype is also accompanied by the generation of extrachromosomal telomere repeat fragments [43,44]. Extrachromosomal telomeric DNAs were also found in cells from patients with ataxia-telangiectasia and ATM-deficient mice, although it was not determined if these were linear or circular [45].

Small polydisperse circular DNAs (spcDNA), derived from a variety of genomic sequences, especially repetitive sequences, are frequently observed in mammalian cells with genomic instability [46]. In some human and rodent cell lines and cancers with spcDNA, double-stranded circular DNA molecules apparently containing only telomeric repeats have been detected [47]. There is no evidence that t-circle formation is under physiological regulation in these pathological cases and it may result from unregulated recombination. T-circles have also been found to occur normally in at least some vertebrate cells. In *Xenopus laevis*, it was shown that their amount is regulated during development and reaches its peak (~10% of the total cellular telomere content) in the early embryonic stage [48]. While their significance remains unclear, the presence of t-circles in various vertebrate models suggests that they may be involved in telomere dynamics under both normal and pathological circumstances.

Telomeric nanocircles, synthetic 54 nt single-stranded DNA molecules constructed of telomeric repeats, can be used as templates for rolling-circle DNA synthesis in vitro [35]. Interestingly, in the presence of a DNA polymerase such nanocircles can give rise to products in a telomere repeat amplification protocol (TRAP) assay similar to those generated by telomerase. This mimicry of telomerase may lead to false-positive results with the TRAP assay in telomerase-deficient cells employing recombination for telomere maintenance. As a consequence, the incidence of ALT tumors might be higher than reported [13].

5. t-Circles: more questions than answers

Many key questions about t-circles remain unanswered. For example, how do they form? How often, and by what mechanisms, do they contribute to RTE? Some potential mechanisms for forming t-circles are shown in Fig. 1B. One simple possibility (Fig. 1B, ii) involves invasion of the single-stranded overhang of a telomere into its own double-stranded region to form a telomeric loop (t-loop) structure [49–53]. As has been proposed by Lustig [42], resolution of this recombination intermediate could lead to both shortening of the telomere in question and production of a t-circle. Once t-circles are present in a cell, they could easily be imagined to be templates for rolling-circle DNA synthesis once a complementary priming sequence was annealed (Fig. 1C, iii). Strand invasion of a 3′ overhang from a telomere into a double-stranded t-circle would provide the priming needed to allow the telomere to be directly elongated by copying the circle. Alternatively, some other mechanism for priming might allow rolling-circle synthesis to occur extrachromosomally with incorporation into the telomere occurring at a later step. Of course, elongation of telomeres through any mechanism involving recombination may depend upon those telomeres initially being in an 'uncapped' state, one more subject to DNA damage responses than a properly 'capped' telomere. RTE in many cells may therefore be limited to situations when telomere capping is compromised.

The extent to which t-circles contribute to telomere elongation, even in cells that solely use recombination to maintain telomeres, may prove to be variable and dependent on a variety of factors. These could include t-circle size and abundance as well as the availability of alternative templates (such as a long telomeric repeat tract at another chromosome end) that might permit a recombination event to elongate a telomere. Senescing yeast cells lacking telomerase and having all its telomeres critically short might require a t-circle to spark the appearance of appreciably longer telomeres. On the other hand, in mammalian ALT cells already containing many long telomeres, t-circles might play a more limited role. One prediction, however, is that t-circles, because of their potential for being copied by a rolling-circle mechanism, contribute to RTE to a degree out of proportion to their abundance.

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