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*** Abstract**

Abstract

Telomeres are the specialized DNA-protein structures that cap the ends of linear chromosomes, thereby protecting them from degradation and fusion by cellular DNA repair processes. In vertebrate cells, telomeres consist of several kilobase pairs of DNA having the sequence TTAGGG, a few hundred base pairs of single-stranded DNA at the 3' end of the telomeric DNA tract, and a host of proteins that organize the telomeric double and single stranded DNA into a protective structure. Functional telomeres are essential for maintaining the integrity and stability of genomes. When combined with loss of cell cycle checkpoint controls, telomere dysfunction can lead to genomic instability, a common cause and hallmark of cancer. Consequently, normal mammalian cells respond to dysfunctional telomeres by undergoing apoptosis (programmed cell death) or cellular senescence (permanent cell cycle arrest), two cellular tumor suppressor mechanisms. These tumor suppressor mechanisms are potent suppressors of cancer, but recent evidence suggests that they can antagonistically also contribute to aging phenotypes. Here, we review what is known about the structure and function of telomeres in mammalian cells, particularly human cells, and how telomere dysfunction may arise and contribute to cancer and aging phenotypes.

Cancer and aging: The importance of telomeres in genome maintenance

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Abstract

Telomeres are the specialized DNA-protein structures that cap the ends of linear chromosomes, thereby protecting them from degradation and fusion by cellular DNA repair processes. In vertebrate cells, telomeres consist of several kilobase pairs of DNA having the sequence TTAGGG, a few hundred base pairs of single-stranded DNA at the 3' end of the telomeric DNA tract, and a host of proteins that organize the telomeric double and single stranded DNA into a protective structure. Functional telomeres are essential for maintaining the integrity and stability of genomes. When combined with loss of cell cycle checkpoint controls, telomere dysfunction can lead to genomic instability, a common cause and hallmark of cancer. Consequently, normal mammalian cells respond to dysfunctional telomeres by undergoing apoptosis (programmed cell death) or cellular senescence (permanent cell cycle arrest), two cellular tumor suppressor mechanisms. These tumor suppressor mechanisms are potent suppressors of cancer, but recent evidence suggests that they can antagonistically also contribute to aging phenotypes. Here, we review what is known about the structure and function of telomeres in mammalian cells, particularly human cells, and how telomere dysfunction may arise and contribute to cancer and aging phenotypes.

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1. Telomere function affects cellular and organismal phenotypes.

Telomeres are specialized DNA-protein structures that cap the ends of linear chromosomes [1]. The telomeric structure is crucial for protecting linear chromosomes from fusion by cellular DNA repair processes, and thus telomeres are essential for maintaining the integrity and stability of genomes. Dysfunctional telomeres, therefore, can lead to genomic instability. Genomic instability, in turn, is a common cause and hallmark of cancer [2, 3] and has also been proposed to contribute to aging [4].

The functional status of telomeres can have profound effects on the phenotype of cells and, by extrapolation, organisms. Telomeres can malfunction as a consequence of DNA damage, telomere shortening due to repeated cell division (in cells that lack the enzyme telomerase), or changes in telomere-associated proteins, as discussed below. When telomeres are damaged or fail to function, they elicit a DNA damage response, characterized by the binding of DNA damage response proteins to the uncapped telomere [5, 6]. Depending on the cell type, genetic background and extent of telomeric damage, cells can die (generally by apoptosis), undergo a permanent cell cycle arrest (senescence), or acquire chromosomal structural abnormalities (gross genomic mutations) [7-9]. These cellular responses can have important consequences for the organism, particularly for complex organisms such as mammals, which contain both mitotic (capable of cell division) and post-mitotic (incapable of cell division) cells [10].

One of the most important organismal consequences of telomere dysfunction is the development of cancer [7, 11-13], which arises from mitotic cells. Dysfunctional telomeres cause cancer primarily by fueling the genomic instability that permits the emergence of increasingly malignant phenotypes. As malignant tumors develop, however, the resident cancer cells – in order to survive -- must eventually acquire mechanisms to stabilize telomeres and prevent their erosion owing to cell division [14]. Thus, cancer cells frequently reactivate

telomerase [15], or acquire an alternative mechanism for maintaining telomeres [16]. In addition, there is increasing evidence that dysfunctional telomeres may contribute to the development of aging phenotypes [7, 8, 11, 13, 17, 18]. For example, telomere shortening and/or dysfunction is evident in certain types of vascular disease, wound healing deficits, and immunosenescence [19-23]. Moreover, telomere stabilization may, at least under some circumstances, prevent or delay the development of aging phenotypes in certain tissues [19-26].

How might telomeres contribute to tumor suppression and longevity in complex organisms? The answer to this question is still evolving. Nonetheless, there are now sufficient data to formulate at least broad hypotheses about the relationships among telomere function, cancer and aging.

2. Telomeres are essential genomic elements

Vertebrate telomeres consist of several kilobase pairs of double stranded DNA containing the repetitive sequence TTAGGG, which terminate in 100-200 bases of single stranded TTAGGG at the 3' end (the 3' overhang) [1, 27]. Telomeres are thought to cap chromosome ends by virtue of their ability to form a protected end structure. This end structure may be a lasso-like structure, termed a t-loop, in which the 3' overhang is proposed to circle back and embed in the duplex DNA that comprises the junction between the lasso circle and stem [28] (Fig. 1). Because telomeres enable cells to distinguish the chromosome ends from intrachromosomal double stranded breaks (DSBs), dysfunctional or uncapped chromosome ends are at great risk for degradation, recombination, and/or fusion by cellular DNA repair systems such as non-homologous DNA end-joining (NHEJ) [29, 30]. Telomeric fusions create dicentric chromosomes, which can break during mitosis, thereby creating *bona fide* DSBs, cycles of chromosome bridges, breakage and fusions, and ultimately genomic rearrangements in the surviving cells [31]. Dysfunctional chromosome ends and genomic instability can also

lead to a decrease or an increase in telomere length, which in turn can prematurely engage or delay, respectively, the senescence checkpoint (discussed below). Thus, without functional telomeres, genetic information can become lost, rearranged, or unstable. These genomic changes, in turn, can drive both cancer and aging phenotypes [2-4, 32, 33].

3. Telomere structure

Mammalian telomeres contain anywhere from <1 kb to >50 kb of telomeric DNA, depending on the species, cell type and genetic background [34-38]. Human telomeres, for example, are 10-15 kb in the germline, but somewhat shorter in somatic cells and often much shorter in cancer cells. On the other hand, laboratory mice (*Mus musculus*) have telomeres that frequently exceed 30 kb in length. Moreover, *Mus musculus* telomeres are very heterogeneous, both among individual telomeres within a single cell and from strain to strain. Comparisons of telomere length among mammalian species show that there is very little effect of telomere length *per se* on the rates of aging or development of cancer. Thus, *Mus musculus* and *Mus spretus*, two closely related mouse species, have an approximately 3-fold difference in telomere length, yet have similar life spans and incidences of cancer. On the other hand, human telomeres are similar in length to those of *Mus spretus,* yet humans have a 30-fold longer life span and correspondingly lower incidence of cancer than this mouse species. Current ideas on telomere function suggest that it is the structure, rather than length per se, that determines telomere function [39, 40]. Moreover, only a few dysfunctional telomeres per cell may be sufficient to elicit a cellular response [41, 42].

Human and mouse telomeres have an unusual chromatin structure characterized by extensive arrays of tightly packed nucleosomes that have a shorter repeat size than bulk nucleosomes [43]. This finding suggests that telomeres have unusually dense nucleosomal spacing, a characteristic of heterochromatin. Moreover, mice null for the histone methyltransferases (HMTases) Suv39h1 and Suv39h2, whose functions are required for

heterochromatin formation, show decreased di- and tri-methylation of histone H3 lysine9 (H3-K9) at pericentric chromatin, as well as at telomeres. This epigenetic change results in decreased binding of the HP1 (heterochromatin protein-1) family of proteins to telomeric chromatin, abnormal telomere elongation and genomic instability [44]. These findings support the idea that telomeres are heterochromatic structures and subject to epigenetic regulation [45]. Epigenetic regulation is also believed to be responsible for the Telomere Position Effect (TPE) – the transcriptional silencing of genes near the telomeres [45-47].

The precise structure of mammalian telomeres is not yet known. The 't-loop' structure, in which the 3' overhang loops back on the double stranded telomeric DNA and invades the duplex, was inferred by electron microcopy and indirect biochemical experiments [28, 48] (Fig. 1). This model can explain how the telomeric ends are protected from recognition by the cellular DNA repair machinery. However, other models – for example, end protection simply by the binding of specialized proteins, or a loop structure in which the 3' overhang is sequestered in the interior of the loop but is not embedded in the adjacent duplex – are also possible. Whatever the case, specialized telomere-associated proteins are crucial for forming and maintaining the protective telomeric structure – or cap -- *in vivo*. Of particular interest are the proteins that specifically bind the telomeric DNA repeat sequence or specifically associate with the direct telomeric DNA binding proteins.

4. Telomere associated proteins

4.1 Telomeric DNA binding proteins.

To date, three telomere-associated proteins that bind directly and specifically to telomeric DNA have been identified in mammals. These proteins are TRF1, TRF2 and POT1.

TRF1 and TRF2 each form homodimers that bind the double stranded TTAGGG repeat sequence [49]. POT1, by contrast, binds the single stranded TTAGGG overhang [50] Thus,

minimally, mammalian telomeres are occupied by the direct binding of three sequence-specific binding proteins, namely TRF1, TRF2 and POT1 (Fig. 1). As discussed below, these proteins form a scaffold upon which a host of other proteins, which have both telomeric and non-telomeric functions, associate with the telomeres. To date, the direct telomeric DNA binding proteins TRF1, TRF2 and POT1 have been found exclusively at telomeres. All three proteins appear to be essential and crucial regulators of telomere structure, capping and length control. It is not yet clear whether these proteins reside in a common complex or separate complexes. However, as discussed below, at least one telomere-associated protein that does not bind DNA, TIN2, forms complexes with all three proteins, raising the possibility that TRF1, TRF2 and POT1 may form a single complex that regulates telomere structure.

4.2 Telomere-associated proteins with primary telomeric functions.

TRF1, TRF2 and POT1 each bind several proteins that do not bind telomeric DNA, yet nonetheless appear to have telomere-specific functions. Thus far, these telomere-associated proteins appear to act primarily to modulate the ability of TRF1, TRF2 and POT1 to control telomere structure, function and length.

TRF1 almost certainly regulates telomere structure via its interactions with other proteins. Among the most important of these interactions are its ability to bind the telomere-associated protein TIN2 [51, 52]. TIN2 does not bind telomeric DNA directly. Rather, TIN2 appears to tether TRF1 to POT1 by binding the bridge protein PTOP/PIP1 [53, 54] (Fig. 2). Because there is no evidence that TRF1 interacts with telomerase components or regulates telomerase activity directly, the structure formed by the TRF1-TIN2-PTOP/PIP1 complex is thought to negatively regulate telomere length by indirectly limiting the accessibility of telomerase, the ribonucleic-protein reverse transcriptase that can add telomeric repeat sequences directly to the 3’ overhang [55]. Thus, TRF1, TIN2 and associated proteins may promote a “closed” telomeric structure, or cap, that restricts telomerase from gaining access to

its substrate, the 3' overhang (Fig. 2). This 'closed' telomeric structure is thought to ensure telomere function – i.e., protection from degradation and/or cellular end-joining and recombinational DNA repair processes [39]. TRF1 also interacts with the telomere length-control protein PINX1 (Fig. 2). PINX1 may likewise limit telomere elongation indirectly, by modulating the influence of TRF1 on telomere structure. However, it is possible that PINX1 have other direct effects on telomere length, as it also binds the telomerase catalytic subunit (hTERT in humans) [56].

TRF2 may have a more direct role than TRF1 in modulating telomere structure because it has been shown to be crucial for the formation of t-loop structures, at least *in vitro* [28, 57]. Moreover, consistent with the *in vitro* results, overexpression of dominant negative forms of TRF2 appears to induce pervasive telomere uncapping in human and rodent cells [40, 57-59]. Recently, TIN2 was found to bind TRF2 [60], in addition to directly interacting with TRF1 [51, 52] (Fig. 2). The TIN2-TRF2 interaction is very likely crucial for both TRF2 and TRF1 functions *in vivo*. Depending on the level of expression and type of mutation, dominant negative forms of TIN2, like dominant negative TRF1, can extend telomere length [51], or, like dominant negative TRF2, can induce pervasive telomere uncapping [60]. Thus, TIN2 may link the functions of TRF1 and TRF2. In addition to binding TIN2, TRF2 also binds RAP1 [61], the mammalian homologue of the yeast direct telomere binding proteins Rap1p (*Saccharomyces cerevisiae*) [62]and Taz1 (*Schizosaccharomyces pombe*) [63]. However, in contrast to Rap1p and Taz1, human RAP1 does not bind telomeric DNA directly, but rather associates with telomeres indirectly by binding TRF2 (Fig. 2).

In yeast, a single direct double stranded telomere binding protein (Rap1p or Taz1) is the principal regulator of both telomere length and structure/capping, suggesting that these processes are coordinated. In mammals, however, the two direct double stranded telomeric DNA binding proteins, TRF1 and TRF2, do not directly interact with each other [49].

Nonetheless, perturbations to either TRF1 or TRF2, or their associated proteins POT1, RAP1 or TIN2, influence both telomere length and capping [50, 51, 60, 61, 64-67], suggesting that the activities of TRF1 and TRF2 are coordinated. Since TIN2 thus far is the only protein known to interact with both TRF1 and TRF2, TIN2 may coordinate the functions of TRF1 and TRF2. This idea is consistent with the fact that TIN2 homologues are not found in lower organisms, such as yeast, fruit flies (*Drosophila melanogaster*) or nematodes (*Caenorhabditis elegans*), which also appear to have only a single telomeric DNA binding protein. Thus, TIN2 may have evolved concurrently with TRF1 and TRF2 to coordinate their functions.

A major gap in our knowledge of telomere composition is how the myriad proteins that associate with telomeres (Fig. 3) organize. Thus, it is not yet clear whether there is a single TIN2 complex, which always contains TRF1 and TRF2 and their interacting proteins (PTOP/PIP1, POT1, RAP1, PINX1), or whether TIN2 forms multiple complexes, some of which contain TRF1, while others contain TRF2 (Fig. 2). It may well be that different complexes form, depending on whether the telomeric DNA is organized as a linear stretch or the presumptive circle that protects the 3' end.

4.3 Telomere-associated proteins with non-telomeric functions.

TRF1 and TRF2 also bind a number of proteins that are known or thought to have non-telomeric functions, in addition to their presumed functions at telomeres. TRF1, for example, binds two highly related poly-ADP ribosylases (PARPs), TANK1 and TANK2 [68, 69] (Fig. 3). Although the TANKs can be found at telomeres, and even ADP-ribosylate TRF1 *in vitro* [68, 70], these proteins reside predominantly in Golgi-type vesicles, and have also been identified at centrosomes [69, 71-73]. The precise functions of TANKs are not known. The majority of endogenous TANKs reside outside the nucleus, where they interact with the Grb14 adaptor protein and/or IRAP in GLUT4 vesicles [69, 71, 73], but the functional consequences of these interactions is not known. At telomeres, one function of TANKs might be the inactivation

by ADP-ribosylation of TRF1. TANK-mediated ADP-ribosylation causes TRF1 to dissociate from telomeric DNA *in vitro* [68]. Moreover, when nuclear-targeted TANK1 is overexpressed in telomerase-positive human cells, telomeres elongate, consistent with TANKs inactivating TRF1 *in vivo* and TRF1 being a negative regulator of telomere length [70, 74].

Both TRF1 and TRF2 also interact with several DNA repair proteins (Fig. 3), although the functional significance of these interactions is not yet completely understood. Both TRF1 and TRF2 interact with Ku [75-77], the DNA end-binding protein that is crucial for NHEJ [78]. In addition, TRF2 interacts with several proteins that participate in DNA damage sensing or repair, including the RAD50-MRE11-NBS1 (RMN) complex [79], which is crucial for homologous recombinational repair (HR) and may also participate in NHEJ [80]. TRF2 also interacts with the DNA damage sensing protein ATM, and is thought to inhibit ATM activity specifically at telomeres [81], and WRN [82], the protein that is defective in the human premature aging and cancer-prone disorder Werner syndrome [83, 84]. WRN encodes a DNA helicase and exonuclease [85, 86] that appears to participate in both the NHEJ and HR DNA repair pathways [87-94]. It is not known whether all TRF1 complexes contain TANK1/2 and/or Ku, or whether all TRF2 complexes contain ATM, WRN, the RMN complex and/or other DNA damage sensors or repair proteins (Fig. 3).

What are the roles of DNA repair proteins at telomeres? One possibility is that telomeres are storage sites for DNA repair proteins – sites from which these proteins can be readily mobilized upon damage to the genome, as demonstrated in yeast [95, 96]. Alternatively, or in addition, the repair proteins, in concert with the telomere-associated proteins with which they interact, may suppress the inappropriate fusion or recombination of telomeres. In support of this possibility, mammalian cells deficient in Ku, components of the RMN complex, or WRN all show an increase in telomere erosion, fusions or other signs of dysfunction [80, 97-99].

5. Mechanisms of telomere disruption.

As note above, telomeres can become dysfunctional via several mechanisms. Perhaps the most common mechanism is shortening due to the end-replication problem. In humans, most somatic cells in the adult do not express telomerase. Owing to the biochemistry of DNA replication, the 3' ends of linear DNA molecules cannot be completely replicated [14]. Thus, dividing cells progressively lose telomeric DNA. When telomeres become critically short, they fail to function as caps or end-protection, causing replicative senescence or cell death [8]. Telomeres can also malfunction as a consequence of direct damage. Several lines of evidence suggest that telomeres are especially susceptible to oxidative DNA damage [100, 101], which may be the major source of DNA damage in mammalian organisms [102-104]. Finally, mutations that alter the expression or function of any of the telomere-associated proteins can also cause telomeres to malfunction.

6. Consequences of telomeres disruption.

6.1 DNA damage response.

What happens when telomeres fail to function? As noted above, dysfunctional telomeres appear to be sensed by cells as damaged DNA, specifically DNA having a DSB. Thus, dysfunctional telomeres -- whether generated by replication-dependent shortening [5, 105, 106], expression of dominant negative TRF2 [6], or expression of dominant negative TIN2 [60] -- induce a classic DNA DSB response. These telomeric DNA damage foci contain phosphorylated histone H2AX (γ-H2AX) and a variety of other DNA damage response proteins such as the DNA damage inducible kinases (ATM, ATR, DNA-PK, CHK1 and CHK2), the RMN complex and the BRCT motif proteins MDC1/NFBD1 and 53BP1 [42, 105, 107, 108] (Fig. 4). Because these foci persist, they are thought to be similar or identical to unrepaired DNA breaks, which, interestingly, were recently shown to accumulate with age in mice [106].

6.2 Cellular tumor suppressive responses.

Dysfunctional telomeres, like any irreparable DNA damage, put cells at great risk for genomic instability and, hence, puts the organism at risk for developing cancer. Therefore, dysfunctional telomeres elicit the cellular tumor suppressor mechanisms of apoptosis or senescence [58-60]. Whether cells undergo apoptosis or senescence in response to telomere dysfunction depends on the cell type and genetic background, notably the p53 status of the cell.

Apoptosis, or programmed cell death, literally eliminates cells at risk for neoplastic transformation. Senescence, by contrast, permanently arrests their growth. Both processes are controlled by the p53 tumor suppressor protein [109-113]. p53 is a transcriptional regulator that both transactivates and transrepresses target genes in response to stress [114, 115]. These target genes, in turn, stimulate DNA repair, transient cell cycle arrest, permanent cell cycle arrest (senescence) or cell death (apoptosis), depending on cell type, degree and type of damage, and other variables. In contrast, cells that lack normal p53 regulation or function – for example, tumor cells – tend to die in response to telomere dysfunction. Some normal human cells, on the other hand, undergo a senescence growth arrest. In either case, when present, p53 is crucial for mediating the cellular response to telomere dysfunction [9, 18, 109, 111, 116, 117] (Fig. 4).

7. Impact on cancer

The cellular tumor suppressor mechanisms ensure that cells with persistent telomere dysfunction do not divide. Cell division under such circumstances would almost inevitably exacerbate the genomic damage. Prior to mitosis, dysfunctional telomeres are fused to each other or any DNA break resulting in translocations or, worse, intrachromosomal breaks as dicentric chromosomes are ripped apart during mitotic segregation. The latter scenario leads to cycles of fusion and breakage, and hence genomic instability – a hallmark of cancer cells [2, 3, 118-120]. Cells that have lost the tumor suppressor responses of apoptosis or senescence –

for example, owing to mutations or other lesions in the p53 pathway – and develop dysfunctional telomeres – for example, owing to repeated replication or oxidative damage –are then at great risk for neoplastic transformation (Fig. 4). It is important to note, however, that even in cells that have lost p53 or other checkpoint functions, potential cancer cells must acquire a means to eventually stabilize their telomeres and prevent relentless loss of genetic information and organization. Most frequently, this is achieved by the reactivation of telomerase [15], but it is also possible to stabilize telomeres by recombinational pathways [121]. Thus, telomeres can both suppress and facilitate cancer. That is, as validated in mouse models, while telomere dysfunction can fuel the genomic instability that facilitates cancer progression, it must also be resolved in order for cancer cells to survive [122-124].

In summary, functional telomeres are crucial for preventing genomic instability and therefore for preventing cancer. Should telomeres malfunction or otherwise fail, the cellular tumor suppressor mechanisms of apoptosis or senescence are engaged. These responses effectively prevent cells with dysfunctional telomeres from attempting cell division, thereby greatly reducing the risk of cancer (Fig. 4). It is only in cells that have lost the checkpoint functions that engage apoptosis and senescence that telomere dysfunction can lead to the genomic instability that fuels cancer. Thus, the link between telomere function and cancer is both strong and relatively straightforward. In contrast, the link between telomere function and aging is still an area of active investigation, and is likely to be indirect.

8. Impact on aging

There is no straightforward relationship between telomere length or stringency of control of telomerase expression and organismal life span [34]. On the other hand, two human syndromes with features of premature aging – Werner syndrome (WS) and dyskeratosis congenita (DKC) – have been linked directly (DKC) or indirectly (WRN) to telomere length and presumably telomere structure [125, 126]. Thus, functional telomeres may directly increase

longevity by maintaining genomic stability and suppressing cancer while also indirectly postponing aging phenotypes by preventing apoptosis and/or senescence [10, 13, 113]. Whatever the case, the cellular responses to telomere dysfunction – apoptosis and senescence – have been proposed to contribute to aging phenotypes [10].

The idea that cellular tumor suppressor responses to telomere dysfunction – apoptosis and senescence – might contribute to aging may seem paradoxical. Why might a tumor suppressor mechanism, which surely evolved to promote longevity by preventing cancer, promote aging? A likely answer is that apoptosis and senescence may be examples of evolutionary antagonistic pleiotropy [10, 13, 113, 127]. According to this evolutionary hypothesis [128], traits that clearly benefit the fitness of young organisms – tumor suppression, for example -- can have unselected deleterious effects late in life. These deleterious effects manifest themselves only late in the life span, after the force of natural selection has declined to negligible levels. Thus, the antagonistic pleiotropy hypothesis predicts that some processes that are beneficial to young organisms can also be detrimental to old organisms.

How might apoptosis and senescence be antagonistically pleiotropic and contribute to aging? In the case of apoptosis, this process clearly is beneficial because it culls damaged or defective cells from tissues. However, it also eventually depletes tissues of cells and/or depletes stem cell reserves. In the case of senescence, this process is beneficial because it prevents the proliferation of preneoplasic, damaged or defective cells. However, senescent cells persist and adopt an altered phenotype in conjunction with the senescence growth arrest [127, 129, 130]. This phenotype includes the secretion of degradative enzymes, cytokines and growth factors that can perturb the surrounding tissue, leading to a loss of tissue homeostasis and development of age related pathologies.

In summary, functional telomeric structures help maintain the stability of the genome (prevent cancer) and protect cells against telomere- induced apoptosis or senescence (postpone aging) (Fig. 4). On the other hand, dysfunctional telomeres lead to genomic instability, which can promote cancer, but also lead to the tumor suppressor mechanisms of apoptosis and senescence, which can promote aging (Fig. 4). Therefore, telomeres act in context, and can balance their ability to prevent or promote complex organismal phenotypes such as cancer and aging.

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Figure legends

Figure 1 Core telomeric structure: Telomeric DNA repeats are associated with the direct telomeric DNA binding proteins TRF1, TRF2 and POT1 to form a core telomeric structure.

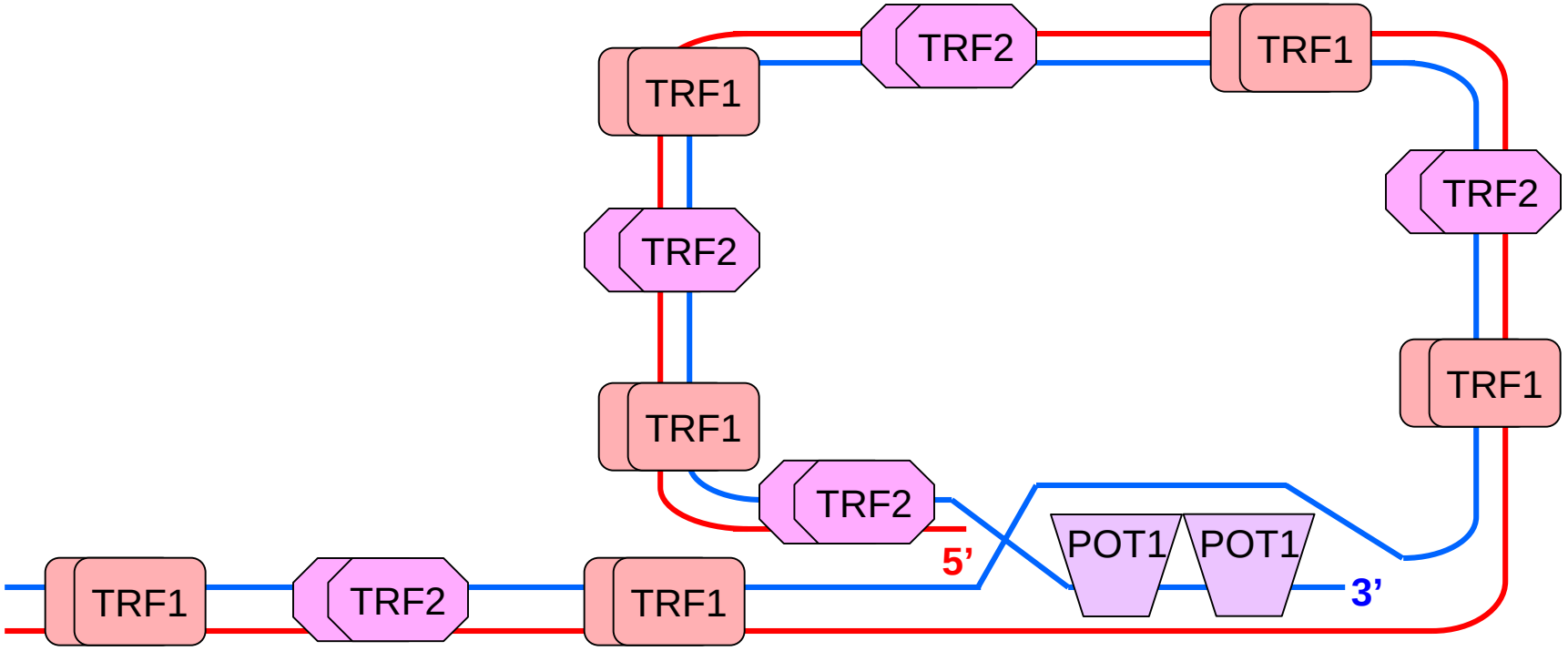
Figure 2 Telomeric capping structure: The core telomeric structure recruits other essential organizers that do not interact directly with the telomeric DNA but are important for telomere capping.

Figure 3 The extended telomeric cap: The telomeric capping structure recruits myriad other proteins, such as the TANKs and DNA repair proteins that also have specific functions elsewhere in the cell.

Figure 4 The outcome of telomere dysfunction includes the generation of a persistent DNA damage signal. The fate of cells that experience this signal, genomic instability, senescence or apoptosis, depends critically on p53. This cell fate subsequently influences the organismal phenotypes of cancer and aging.

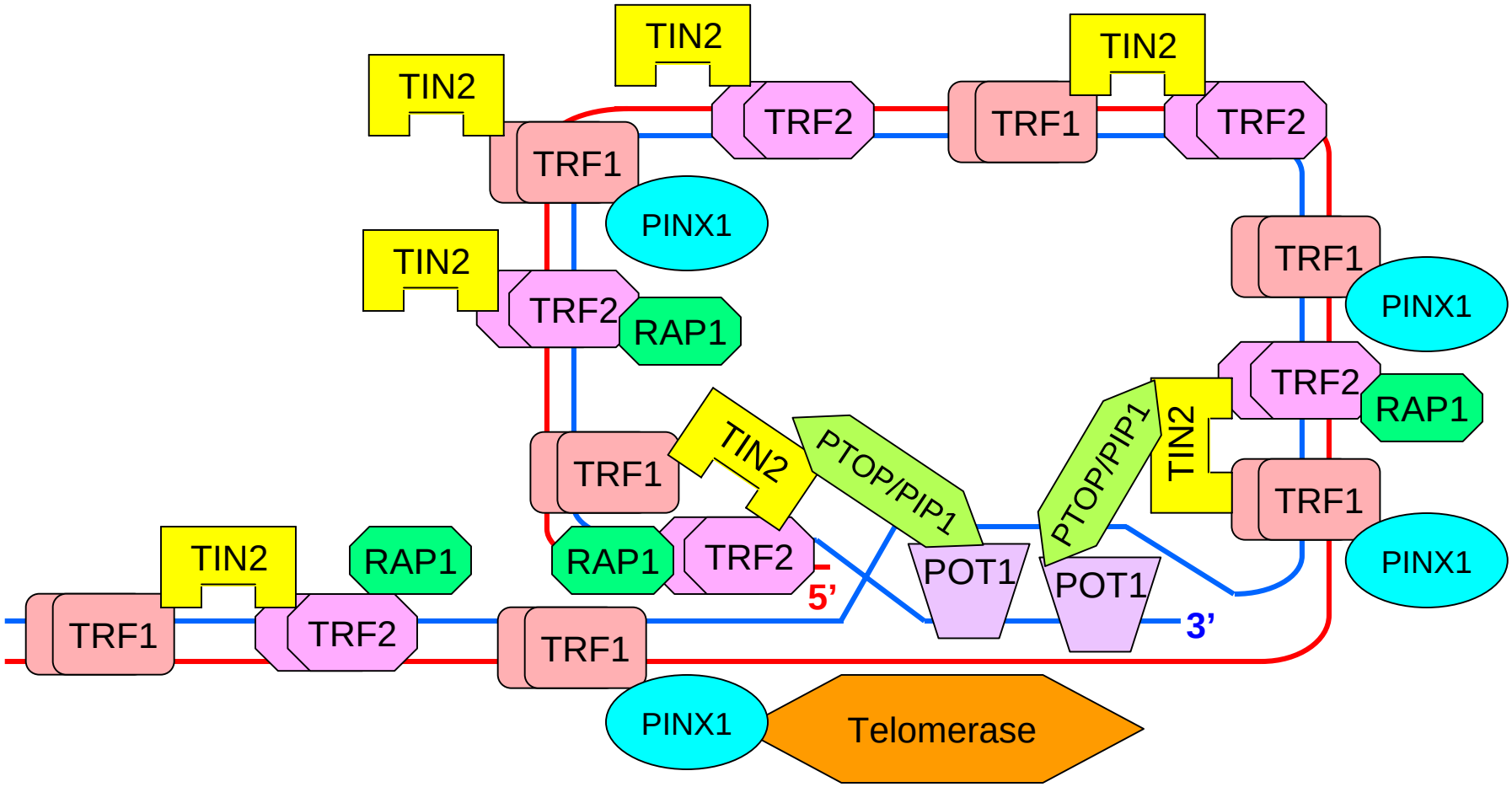
Figure(s)

Rodier et al, Figure 1



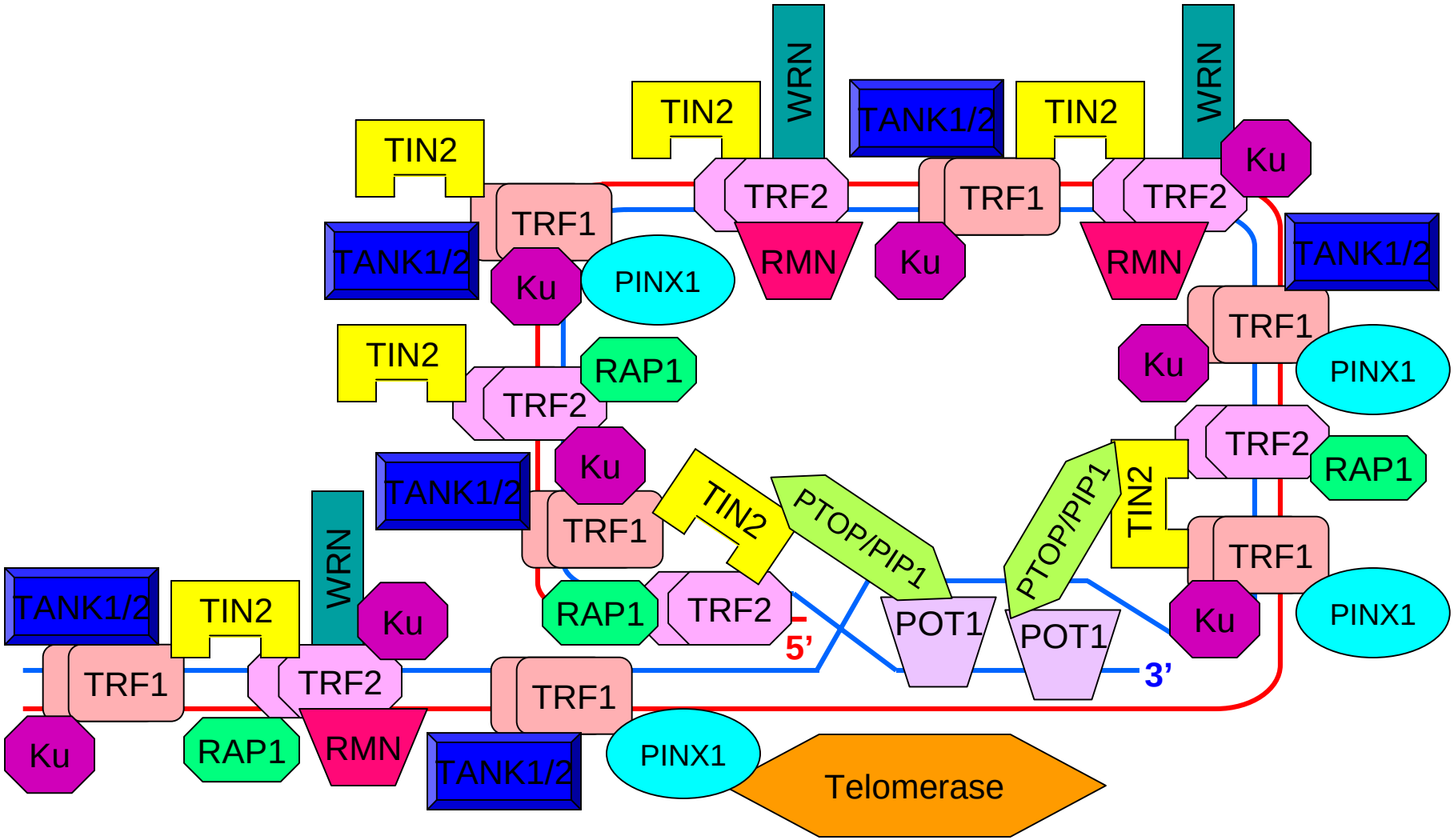
Figure(s)

Rodier et al, Figure 2



Figure(s)

Rodier et al, Figure 3



Figure(s)

Rodier et al, Figure 4

