Published in final edited form as:
Exp Cell Res. 2013 January 15; 319(2): 133–141. doi:10.1016/j.yexcr.2012.09.005.

Telomeres - Structure, Function, and Regulation

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Abstract

In mammals, maintenance of the linear chromosome ends (or telomeres) involves faithful replication of genetic materials and protection against DNA damage signals, to ensure genome stability and integrity. These tasks are carried out by the telomerase holoenzyme and a unique nucleoprotein structure in which an array of telomere-associated proteins bind to telomeric DNA to form special protein/DNA complexes. The telomerase complex, which is comprised of telomeric reverse transcriptase (TERT), telomeric RNA component (TERC), and other assistant factors, is responsible for adding telomeric repeats to the ends of chromosomes. Without proper telomere maintenance, telomere length will shorten with successive round of DNA replication due to the so-called end replication problem. Aberrant regulation of telomeric proteins and/or telomerase may lead to abnormalities that can result in diseases such as dyskeratosis congenita (DC) and cancers. Understanding the mechanisms that regulate telomere homeostasis and the factors that contribute to telomere dysfunction should aid us in developing diagnostic and therapeutic tools for these diseases.

Keywords

telomere; telomerase; telosome; telomere maintenance; end protection; extra-telomeric; telomere dysfunction

Introduction

In the 1930s, by comparing X-ray generated break ends of chromosomes to natural ones in fly and maize, Muller and McClintock concluded that natural chromosome ends could shield chromosomes from rearrangement/fusion events that often occurred between intra-chromosomal breaks [1, 2]. Later studies in *Tetrahymena* and yeast showed that the

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chromosome ends were protected by tandem repeats of hexanucleotide units that could function across species, suggesting evolutionary and functional conservation [3–6]. In the mid-1980s, the seminal work from Blackburn and Greider, which demonstrated the existence of an enzymatic activity within cell extracts that added tandem hexanucleotides to natural chromosome ends, eventually led to the discovery of telomerase [7]. And the past decade has seen leaps and bounds in our understanding of the various components in controlling telomere homeostasis [8–12].

Telomere maintenance requires the telomerase and a network of telomere-associated proteins, and necessitates the inhibition of various DNA-damage response (DDR) signals that include ATM and ATR pathways, homologous recombination (HR), and non-homologous end joining (NHEJ) (Figure 1) [13]. Indeed, genetic and epigenetic aberrance in telomere-associated proteins, telomerase, and epigenetic enzymes, can result in abnormal telomere length, telomere damage induced foci (TIF), telomere end-end fusion, and ultimately cell cycle arrest, senescence, and genome instability [13, 14]. In human, telomere dysfunction has been implicated in bone marrow failure syndromes, leukemia, and cancer development [9, 10, 15–17]. Understanding the mechanisms by which telomeric DNA, telomerase, and telomere-interacting proteins function together will undoubtedly facilitate the development of diagnostic and therapeutic tools for telomere-relevant diseases. In this review, we will focus mainly on the achievement and progress made in telomere biology by Chinese scientists.

1. Telomere structure and maintenance

1) Telomeric DNA and G-quadruplex—Telomeres are comprised of repeat sequences and bound by multiple telomeric interacting proteins. In mammalian cells, telomere DNA contains double-stranded tandem repeats of TTAGGG followed by terminal 3′ G-rich single-stranded overhangs. Telomere DNA is thought to adopt the T-loop structure, where the telomere end folds back on itself and the 3′ G strand overhang invades into the double-stranded DNA (the so-called D-loop) [8].

Because of its enriched G content, the single-stranded telomere G overhangs can form G-quadruplexes, where each G base serves as both donor and acceptor for hydrogen bond formation. In human, telomeric G-quadruplex structures have been implicated in telomere protection, suppression of recombination, and inhibition of telomerase-dependent telomere extension [18]. Tan and colleagues from Institute of Zoology at Chinese Academy of Sciences have been systematically exploring the impact of different physical and chemical conditions on the stability of the telomeric G-quadruplex. For instance, they have observed that human telomere DNA forms a parallel-stranded conformation under molecular crowding conditions that mimic physiological environment [19]. Using different approaches including a real-time fluorescence assay, the group provides evidence that the unwinding of intramolecular telomere G-quadruplex structures by BLM and other RecQ family of helicases would be more difficult than unwinding of duplexes, supporting the role of G-quadruplexes in telomere protection [20].

Previous work has demonstrated that four TTAGGG repeats can fold into a G-quadruplex and influence telomere elongation *in vitro*, suggesting that G-quadruplexes are poor

substrates for the telomerase [21]. By DMS footprinting and exonuclease hydrolysis, the Tan group showed that the G-quadruplex preferentially forms at the very 3′ end of telomeres where it may inhibit telomerase accessibility for telomere extension [22]. End processing enzymes such as telomerase and helicases likely require a free single-stranded 3′ telomere end. By analyzing the size of the 3′ tails required for different end reactions, Tan and his colleagues have demonstrated that a minimal tail of 6, 8, and 12nt is required respectively for telomere G-quadruplex unwinding, telomere extension by telomerase, and the alternative lengthening of telomere (ALT) mechanism [23]. Due to the farthest 3′ distal end of telomere DNA leaving a tail of ≤5nt, their study also suggests that telomere G-quadruplexes may regulate the aforementioned end reactions at chromosomal ends [23]. Taken together, telomere G-quadruplex structures regulate the action of multiple enzymes, including the telomerase, at the very end of chromosomes for telomere length regulation and end protection, and may therefore serve as a potential drug target for aging and cancer therapies.

In yeast, the telomerase subunit Est1p has recently been shown to be capable of converting single-stranded telomeric G-rich DNA into a G-quadruplex structure *in vitro* in a magnesium-dependent manner, and required for telomerase-mediated telomere protection [24, 25]. In these studies by the Zhou group, Est1p mutants can disrupt G-quadruplex *in vitro* and lead to telomere shortening and cellular senescence *in vivo*, suggesting a positive role for G-quadruplex in telomere length regulation [24]. It is clear that further studies are required to tease out the functional differences of G-quadruplex in regulating telomerase and telomere length between human and other organisms.

The length of 3′ G-overhang is critical for end processing and telomerase regulation. Taking advantage of a double-strand specific nuclease (DSN), Zhao *et. al.* developed an approach to measure the exact size of single-stranded 3′ G overhangs, thus providing a novel tool for telomerase studies [26]. This study also revealed that the length of G overhangs of lagging strands appeared longer than those of leading strands in human BJ cells [26]. It should be noted that the telomerase is thought to be preferentially recruited to the shortest telomeres for length maintenance [27]. Recent work from Zhao *et. al*. challenges this model by showing that telomerase extends most chromosome ends during each S phase and uncouples from subsequent C-strand fill-in process in human cancer cells. These findings suggest step-wise telomere maintenance pathways and may open up a new avenue of research for anti-telomerase therapeutics [28].

2) Telomerase and its regulation—The telomerase is a unique ribonucleoprotein complex that consists of the telomerase reverse transcriptase (TERT), and a telomerase RNA component (TERC) that serves as the template for telomere extension during *de novo* addition of TTAGGG repeats onto chromosome ends (Figure 1) [29]. While TERC expression is ubiquitous, TERT expression appears highly regulated. For example, telomerase is expressed in stem cell compartments and in embryonic stem cells, but TERT expression and telomerase activity are often very low or undetectable in somatic cells [30]. In contrast, in most cancer cells (85–90%) telomerase activity appears elevated [31–33]. In mice, deletion of either TERC or TERT leads to telomere shortening, genomic instability, aneuploidy, telomeric fusion, and aging-related phenotypes [34, 35]. In comparison, overexpression of TERT can dramatically increase the life span of mice in the context of

overexpressing tumor suppressor genes such as p53, p16, and p19 [36]. Therefore, telomerase dysfunction may result in defects in various highly proliferative cells/tissues and ultimately lead to degenerative diseases, such as dyskeratosis congenita (DC).

Following the cloning and complete sequencing of human TERT (hTERT) [37], extensive efforts have shifted to studying how TERT expression is regulated. With a focus on the effects of a variety of factors on telomerase regulation, Liu and colleagues have found that the C-terminus of p53 interacts with the N-terminus of human telomerase-associated protein 1 (hTEP1) and inhibits telomerase activity *in vitro* [38]. In agreement with this finding, p53 has been shown to interact with SP1 and inhibit its targeting to the hTERT promoter for transactivation [39]. They also showed that nerve growth factor (NGF)-induced inhibition of telomerase occurred in a MAP kinase signaling-dependent manner in PC12 phenochromocytoma cells [40], and the TGF-beta signaling downstream transcription factor Smad3 can be recruited to the TERT promoter for transcription repression [41]. Further studies have demonstrated that bone morphogenetic protein-7 (BMP7) induces Smad3 phosphorylation, nuclear translocation, and hTERT gene repression, resulting in telomere shortening, tumor growth arrest, senescence, and cell death [42, 43]. More recently, the Liu group discovered that, under oxidative stress, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) could interact with TERC and lead to the inhibition of telomerase activity, telomere shortening, thereby inducing cancer cell senescence [44].

Epigenetic modification of histones can modulate chromatin structure and accessibility of the transcriptional machinery to regulatory regions of target genes. Based on reporter assays and results from using the histone deacetylase inhibitor trichostatin A (TSA), histone deacetylation has been suggested to repress hTERT expression by modulating histone acetylation on the TERT promoter in human cells [45]. In addition, numerous transcription factors, such as c-MYC, SP1, MAD1, and HIF-23, have been shown to recruit either histone acetyltransferases (HATs) or histone deacetylases (HDACs) to the promoter of TERT to control its expression [46–48]. Interestingly, the Xu group showed that histone H3K4 methyltranferase SMYD3 and histone demethylase LSD1 together with HDACs could directly activate and repress TERT expression, respectively [49, 50]. Furthermore, MAD1 has been shown to recruit RBP2 (H3K4 demethylase) to TERT promoter for its repression [51]. Recent work from Xu and colleagues also indicates that MAP kinase cascade-mediated phosphorylation of histone H3 Ser10 at the TERT promoter triggers telomerase transcriptional activation in proliferating cells [52]. Additionally, Song *et. al.* also showed that the systemic environment and stem cell niche are major reasons for the impairment of lymphopoiesis in aging telomerase knockout mice [53], suggesting additional avenues for anti-aging therapy in the context of telomere dysfunction. Taken together, these studies have highlighted unique possibilities of exploring factors from extracellular environment, intracellular signaling cascades, transcription factors, and epigenetic components for anti-aging and anti-cancer therapies.

3) Telomere dysfunction and the p53/p16 pathways—Telomere dysfunction could lead to accumulated damage at the telomeres and cellular senescence and death. In fact, telomere damage is a key factor in cellular senescence [54]. p53 and p16-mediated signaling cascades are two of the critical pathways implicated in telomere dysfunction and cellular

senescence. In particular, work from the groups of Tong and Zhang has been instrumental to our understanding in these widely studied areas. They have carried out pioneer work to reveal connections between p16/p21/p53 regulation, telomere function, aging, and cancer progression [55–58]. The group has recently shown that HDTIC compounds from the traditional Chinese medicine *Astragalus membranaceous* can prevent telomere shortening, enhance DNA repair ability, and delay senescence through attenuating oxidative stress, suggesting new mechanisms and agents for anti-aging therapy [59]. In support of these findings, the Blasco group has also shown that TA-65, a small molecule from *Astragalus membranaceous*, is capable of activating the telomerase, elongating telomeres, inhibiting DNA damage, and extending tumor-free life-span of mice [60].

4) Telomeres and pluripotency—Pluripotent cells such as embryonic stem cells (ESC) and induced pluripotent cells (iPSC) hold unrivaled promise for regenerative medicine, and have been the subjects of intense studies including those that focus on the role of telomeres in developmental pluripotency. For instance, the Liu group from Nan Kai University showed that ESCs with long telomeres exhibited *bona fide* developmental pluripotency, in terms of generating complete ESC pups and germline-competent chimeras [61]. These observations suggest that functional telomeres are essential for maintaining pluripotency in ESCs/iPSCs, and possible markers for evaluating pluripotency. Using iPSCs derived from telomerase-deficient cells, the group went on to demonstrate that telomerase plays a critical role in reprogramming and self-renewal of iPSCs [62]. Moreover, telomerase re-activation appears to occur earlier than pluripotent genes (Oct4 and Nanog) during reprogramming, suggesting that telomere regulation is both a critical step for generating pluripotency and essential for maintaining stem cell-based tissue homeostasis [62].

2. The Telomere Interactome – protein-protein interacting networks at telomeres

Telomere maintenance relies on a vast network of protein complexes at the telomeres. Central to this process is a six-protein complex (Figure 1), known as the telosome or shelterin [63, 64]. The telosome is composed of the telomeric repeat-binding protein 1 and 2 (TRF1 and TRF2), the TRF1-interacting protein 2 (TIN2), RAP1, protection of telomeres 1 (POT1), and TPP1 [63, 64]. TRF1 and TRF2 share a common domain structure consisting of a N-terminal TRFH domain, and a C-terminal SANT/Myb domain with high binding specificity for the half site 5′-YTAGGGTTR-3′ in telomeric double-stranded DNA (dsDNA) [64]. The two N-terminal OB-folds of POT1 are highly specific for the 5′-TAGGGTTAG-3′ sequence of single-stranded G-overhangs [65]. TIN2 serves as a hub to bridge various telosome components by directly binding to TRF1, TRF2, and the TPP1/POT1 heterodimer [11]. TPP1 directly interacts with TIN2 and POT1 as well as the telomerase [11, 66]. Mammalian RAP1 is targeted to telomeric DNA by directly interacting with TRF2 [11].

Together, the six core proteins function as the platform that recruits players from diverse pathways to the telomeres for maintenance and protection. This is evident in a recent study from our group where we carried out a BiFC-based genome-wide screen for interaction partners of the six core telomere proteins in live human cells [12]. We identified >300 proteins, including numerous novel telomere-associated proteins. Thanks to the unique properties of the BiFC strategy, a number of weak/transient telosome interaction proteins,

such as protein kinases and ubiquitin E3 ligases, were identified [12]. These findings underscore the complexity of the telomere maintenance network and the amount of work still needed to understand these pathways.

1) TRF1—The first double-stranded DNA binding protein identified [67], TRF1 acts as negative regulator for telomere length [68]. Homozygous deletion of TRF1 in mice led to embryonic lethality around the blastocyst stage with severe growth defects accompanied by apoptosis [69]. The absence of telomerase could not rescue this phenotype, suggesting essential function of TRF1 that may be independent of telomere length regulation [69]. Through crystal structure analysis, Lei and colleagues demonstrated that TRF1 could recognize TIN2 through its TRFH domain, and the TRFH domain of TRF1 (not TRF2) interacts with PinX1 [70]. Their more recent work further revealed that the atypical GTPase domain of Fbx4 could serve as a substrate-binding motif for the SCF E3 ligase complex and bind to a globular domain of TRF1 for its ubiquitination and degradation. These findings provide clues to the underlying mechanism for controlling TRF1, whose expression is tightly regulated, as well telomere homeostasis [71].

2) TRF2 and RAP1—Originally identified through homology search [72], TRF2 has emerged as a critical player in telomere maintenance – negatively regulating telomere length [73] and participating in telomere end protection. These activities are carried out at least in part through the multitude of factors that interact with TRF2, such as Apollo, ERCC1/XRF, the DNA repair MRN complex, WRN, and FEN1 [70, 74]. Using biochemical approaches, our group and the Lei group discovered that the TRFH domain within human TRF2 could recognize [Y/F]XL peptides with the consensus motif of YYHKYRLSPL [70, 75]. A number of novel TRF2 TRFH interactors were identified based on the binding motif, including phosphatase nuclear targeting subunit (PNUTS) and microcephalin 1 (MCPH1) [75]. We provided evidence that PNUTS and MCPH1 could localize to telomeres, and respectively control telomere length and DNA damage responses at the telomeres [75]. In addition, DDX39 (DEAD-box RNA helicase) has been reported to directly interact with TRF2 via the FXLXP motif and depletion of DDX39 leads to induction of TIF (telomere dysfunction-induced foci), adding another pathway that connects TRF2 to DDR inhibition [76]. It is clear that TRF2 acts as a hub to recruit various factors for telomere regulation. One such example is the ATM-mediated NHEJ pathway. TRF2-deficient MEFs show massive end-to-end fusions mediated by the NHEJ pathway that lead to severe proliferation defects [77]. Similar to TRF1, homozygous inactivation of TRF2 in mice is embryonic lethal. Unlike TRF1, however, the TRF2 lethality cannot be rescued by p53 abrogation, indicating different mechanisms are utilized by TRF1 and TRF2 to ensure survival during embryonic development [77].

RAP1 appears highly conserved, with a RCT domain, a BRCT domain, and Myb domain(s) [8]. Unlike its budding yeast counterpart that can directly bind telomeres through its Myb domain, mammalian RAP1 lacks telomere-binding capacity and depends on its interacting partner TRF2 for telomere localization [8, 78]. Through large-scale affinity purification and mass spectrometry, our group identified numerous DNA repair proteins (Rad50, Mre11, PARP1, and Ku86/Ku70) in the RAP1/TRF2 complex [79]. In fact, recent studies have

shown that the DNA repair factor BTBD12 complexes with TRF2/RAP1 and facilitates Holliday junction processing and DNA damage response, suggesting its potential role at repressing HR at telomeres [80]. In contrast to TRF1 and TRF2, RAP1-deficient mice are viable, although with increased telomere recombination and fragility [81].

3) POT1—POT1 was originally cloned based on sequence homology to the single-stranded G-rich DNA-binding protein in ciliated protozoa [82]. It was later revealed by Lei *et. al*. that the N-terminus of yeast Pot1p (Pot1pN) could adopt an oligonucleotide/oligosaccharide-binding (OB) fold with two protruding loops that form a clamp for ssDNA binding [83]. In comparison, the two OB folds of human POT1 (hPOT1) recognize the telomeric single-stranded DNA (ssDNA) decamer TTAGGGTTAG, with the N-terminal OB fold of hPOT1 binding the first six nucleotides, while the second OB fold binding and protecting the 3′ end of ssDNA [65].

POT1 has been shown to protect telomere ends from ATR-dependent DNA damage response, control 5′-end resection at telomere termini, and regulate telomerase-dependent telomere elongation [84–86]. In contrast to human POT1, mice have two *Pot1* orthologs with distinct function -- *Pot1a* and *Pot1b* [85, 86]. Loss-of-function studies for Pot1a and/or Pot1b in mice and in cells have revealed that Pot1a mainly represses the ATR-mediated DNA damage response, while Pot1b regulates 5′-end resection [85, 86]. Human POT1 is thought to combine the features of mouse POT1a and POT1b [87]. A recent study on mouse Pot1b indicates that it can inhibit excessive 5′-resection by interacting with the CST (Ctc1/Stn1/Ten1) complex during 3′-overhang generation [88]. These observations have led to the current model where POT1 may exclude RPA, major ssDNA binding proteins, for G-overhang binding and thereby inhibit ATR-mediated DNA damage signals. In support of this model, the Zou group recently demonstrated that hnRNPA1, TERRA (telomeric repeat-containing RNA), and POT1 could act together to displace RPA from telomeric ssDNA after DNA replication, and promote telomere end protection [89].

4) TPP1—Our group first identified TPP1 (known as PTOP then) through large-scale affinity purification and found it to interact with both TIN2 and POT1 [90]. Work from us and other groups has since shown that human TPP1 binds to the c-terminus of POT1 and is required for POT1 telomere localization [90–92]. TPP1 turns out to be the mammalian homologue of *Oxytricha nova* TEBP3 and contains an N-terminal OB fold [93]. Indeed, structural analysis revealed the similarities between that human TPP1 OB fold and that of TEBP3, suggesting that the TPP1/POT1 heterodimer is the homolog of TEBP3/3 heterodimer [66]. As is the case for TEBP3/3, TPP1 directly interacts with POT1 and enhances POT1 affinity for telomeric ssDNA [66, 93]. Furthermore, TPP1 directly interacts with the telomerase for its recruitment to telomeres [66, 93]. For example, decreased telomerase binding to telomeres and telomere shortening have been detected in TPP1 null MEFs and mice [91]. Moreover, TPP1-deficient MEFs are unable to be reprogrammed to iPSCs, a process that is dependent on telomerase activity [91]. Notably, in *acd* mice which are spontaneously occurring mutants that are haploid-insufficient for mouse TPP1, growth defects are apparent in various highly proliferative and telomerase-positive tissues, such as hair follicle stem cell compartments [94]. Using the zebrafish model, our group has also

shown that depletion of zfTPP1 leads to multiple abnormalities in embryogenesis, including neural death, heart malformation, caudal defect, and extensive apoptosis, suggesting functional conservation of this protein [95]. Moreover, TPP1 has also been shown to interact with OBFC1/Stn1, an OB-fold protein that directly binds to ss-telomeric DNA, for telomere length control [96]. In fact, a recent study revealed that the OBFC1/Stn1-containing CST complex is involved in 5′-end resection for 3′-overhang generation. And depletion of OBFC1/Stn1 leads to telomere elongation [88, 97]. Taken together, TPP1 is essential for both telomere end protection and length regulation, through repressing ATR-mediated DNA damage signaling and modulating telomerase-dependent telomere elongation.

5) TIN2—By directly interacting with TRF1, TRF2, and TPP1 [11], TIN2 acts as the central component in the telosome complex [98]. Here, TIN2 disruption results in significantly decreased telomere localization of all telosome components, accumulated RPA binding to telomere termini, and increased ATR-mediated DNA damage responses, which also mirror the phenotypes in POT1a/1b double knockout mice [99]. TIN2 deletion in mice leads to embryonic lethality, and data from TIN2-deficient cells further support a role of TIN2 in facilitating TRF2-dependent inhibition of ATM-mediated DDR, and in telomerase recruitment and telomere length regulation [99]. To date, TIN2 is the only telosome component with identified mutations in human diseases. In patients with dyskeratosis congenita (DC), dysfunction in TIN2-dependent telomere length control and TPP1-mediated telomerase recruitment may be manifested. Expression of TIN2 with missense mutations found in DC patients could recapitulate the telomere shortening phenotype observed in patients [100], making TIN2 a possible target for diagnostic and therapeutic studies.

3. Extra-telomeric function of telomere proteins

Non-canonical function of telomerase and telomere proteins has been garnering increasing attention lately. Accumulating evidence suggests a broader role for these proteins outside of the telomeres (Figure 1). For example, human TIN2, TPP1, and POT1 can localize and interact in the cytoplasm [101]. And TRF2 has been implicated in regulating the proliferation and differentiation of neural tumor and stem cells [27, 102, 103]. In fact, TRF2 appears to play an important role in homologous recombination (HR) repair of double-strand breaks at non-telomeric regions [104, 105]. Furthermore, extra-telomeric RAP1 binding sites appeared enriched in subtelomeric regions and in genes deregulated as a result of RAP1 deletion in mouse [81]. Recently, human RAP1 was found to associate with iκB kinases in the cytoplasm and act as a crucial regulator of NF-κB modulated gene expression [107]. Our genome-wide ChIP-seq data on human RAP1 and TRF2 indicate that in addition to telomere sequences, telomere proteins can also target interstitial sites, possibly to regulate transcription [106]. Another group reached similar conclusions through their studies on TRF1 and TRF2 [108]. It has also been reported that the telomerase contains mitochondria targeting signals, and exogenously expressed telomerase can localize to the mitochondria and regulate apoptotic responses to oxidative stress [109–111].

Recently, our group has demonstrated that the N-terminus of TIN2 harbors mitochondrial localization signals, which can target endogenous TIN2 to the mitochondria [112]. Knocking down TIN2 by RNAi led to metabolic changes such as enhanced oxygen consumption and

mitochondrial ATP synthesis, implicating TIN2 in metabolic control. These results point to a novel connection between telomeric proteins and metabolism, and the possibility that TIN2 represents a new factor that may regulate the switch between aerobic glycolysis and oxidative phosphorylation. Further studies may provide additional evidence to link other telomere-associated proteins in addition to TIN2 to metabolism and other extra-telomeric function.

Conclusion

The field has come a long way since the discovery of telomeres and telomerase. With more sophisticated techniques and the convergence of diverse fields, we are gaining a more comprehensive understanding of the pathways and players involved in ensuring telomere integrity. In particular, work from China and Chinese scientists has contributed tremendously to the advancement of telomere-related research. Further work on the mechanisms of telomerase regulation, telomere-binding protein function, and the interplay between telomeres and other cellular compartments should greatly facilitate our understanding of telomere-relevant diseases and our search for appropriate diagnostic and therapeutic tools.

Acknowledgments

We would like to apologize to those whose work cannot be cited here due to space limitations. This work is supported by National Basic Research Program (973 Program 2010CB945400 and 2012CB911200), NSFC 91019020, NCI CA133249, NIGMS GM081627, GM095599, and the Welch Foundation Q-1673. We would also like to acknowledge the support of the Dan L. Duncan Cancer Center (P30CA125123), and the Administrative and Genome-wide RNAi Screens Cores (IDDRC P30HD024064).

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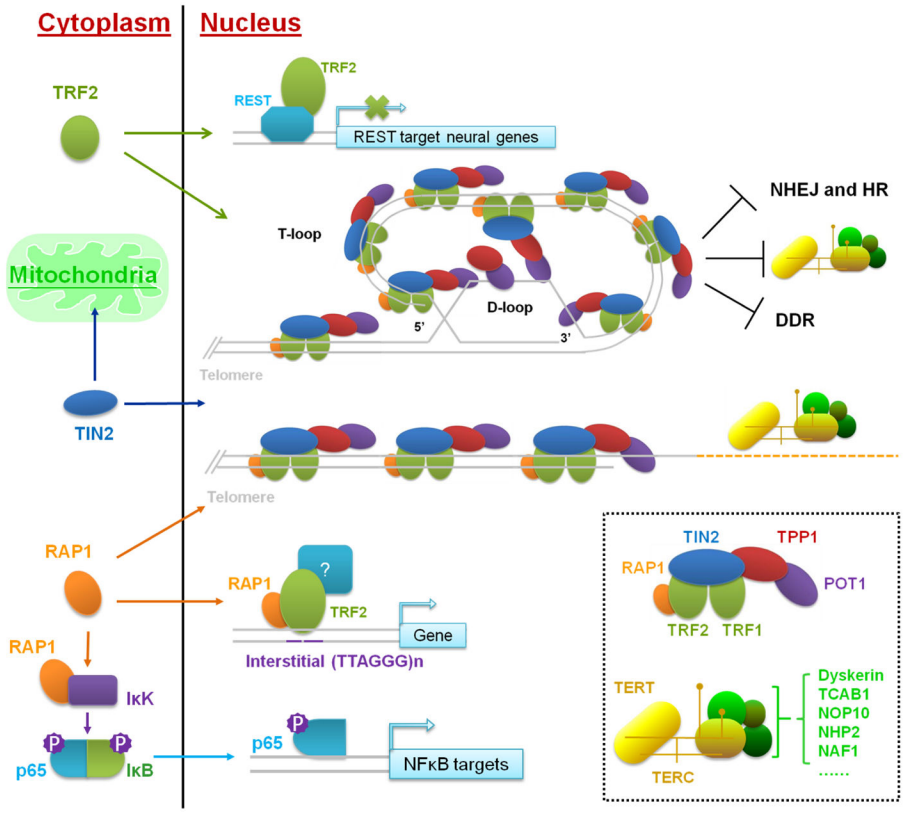

Figure 1.

Canonical and extra-telomeric function of telomere-binding proteins. The six-protein telosome complex and telomerase holoenzyme are depicted in small box. In the nucleus, the telosme and telomerase complex maintain telomere length and protect telomere ends. Several telomere proteins also participate in non-telomeric pathways in the cytoplasm.