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Telomere protein complexes and interactions with telomerase in telomere maintenance

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1. ABSTRACT

Telomeres are the termini of linear chromosomes. They are composed of DNA and DNA-binding proteins critical for maintaining chromosome integrity and cellular function. Telomere binding proteins regulate the structure and function of telomeres through the formation of different complexes with telomeric DNA. Double- and single-stranded telomeric DNA binding protein complexes have shared and unique functions that regulate telomere homeostasis. Recent studies have shown that telomerase interacts with several telomere-binding protein complexes including shelterin, CST, DNA-dependent protein kinase (DNA-PK) and MRN. The present review describes the recognised telomere-binding protein complexes, sub-complex exchanges and inter-complex molecular interactions. It also discusses the evidence suggesting that telomerase reverse transcriptase (TERT) switches between different complexes. Studies of the telomere protein inter-complex interactions and the switching of components between complexes provide insight into their fundamental roles of programming telomere length and configuration, and thus cell proliferative potential.

2. INTRODUCTION

Telomeres, the termini of linear chromosomes, serve the primary function of providing integrity at each chromosomal end in resting and mitotic cells (1-3). This consequently confers both chromosomal stability and a regulatory mechanism during cell division (4). Telomeres achieve their function through interacting with many telomere binding proteins and components of the DNA repair machinery (2). Thus, telomeres prevent undesirable DNA damage and repair activities, and permit spatial-temporal regulation of chromosome ends in a cell cycle dependent manner. Different telomere configurations mediate chromosomal segregation and nuclear organisation and different telomere lengths determine cellular proliferative potential. The loss of telomeric DNA, or associated protein substructures, leads to chromosome instability and inter-chromosomal fusions, culminating in cell death or neoplastic development.

The fundamental roles of telomeres depend on intact telomeric structures that both incorporate and are regulated by telomere binding proteins (5). Telomere

binding proteins coat telomeres in layers regulating telomere configuration and length. In turn, the configuration and number of telomeric repeats influence telomere protein complex formation. The telomere protein complexes form, interact, and disintegrate in response to cellular states such as cell proliferation, differentiation, senescence and immortalisation. Despite the growing body of data, the understanding of telomere-protein interactions is rudimentary.

Recent reviews have covered in detail telomere binding proteins in yeast and humans (5-6), the regulation of telomere lengthening and stabilisation (7), telomeres dynamics in cancer (8-9), alternative lengthening of telomeres (10), the shelterin/telosome complex (11-12) and recruitment mechanisms of telomerase (13-14). Here, we focus on the major telomere protein complexes, including telomere complex interactions, sub-complex switching, and, in particular, the interactions of telomerase with other telomere-binding complexes in mammalian cells.

3. TELOMERE SHORTENING AND LENGTHENING

Human telomeric DNA is comprised of a tandemly repeating sequence of TTAGGG that in humans extends 7-15 kb (1, 15). The G-rich strand of telomeric DNA extends in the 3' direction to form a single-stranded overhang of approximately 150 nucleotides (16-17). The overhang is able to form a lasso-like structure – the telomere loop or 'T-loop' (18-19) – which is thought to serve a protective function (Figure 1). The T-loop is formed when the 3'-overhang invades the telomere duplex and binds to its complementary sequence. The point at which the 3'-overhang resects duplex DNA and inserts itself is termed the 'D-loop' (displacement loop). Formation of the T-loop is partly dependent on the size of the 3' overhang. The telomere erosion associated with loss of 3'overhang lessens the ability to form the T-loop and results in loss of telomere end protection (20).

Telomere shortening accompanies normal somatic cell division due to the 'end replication problem' (21-24) that arises from the use of Okazaki fragments to prime DNA synthesis. On linear chromosomes, the last Okazaki fragment that primes synthesis of the lagging-strand will leave a gap that cannot be filled, leading to incomplete replication of the chromosome (25-26). Hence, human and mouse telomeres shorten at rates between 50 and 150 bp per cell division (27-28). Erosion of telomeres beyond a critical threshold induces permanent exit of the cell cycle. This phenomenon is known as replicative senescence and the number of divisions required to reach it is termed the 'Hayflick limit'. This process was first observed in experiments on fibroblasts, which were shown to have a finite proliferative capacity (29). In humans, telomere shortening is thought to serve as a 'mitotic clock' protecting against inappropriate cellular proliferation that can lead to cancer cell formation. Telomere shortening is also the basis for the 'telomere hypothesis' of ageing (23). Therefore, prolonged proliferation of some cells requires a means of telomere maintenance to stabilise telomere length and prevent the onset of replicative senescence.

To overcome the end-replication problem, highly proliferative cells such as germ line or stem cells express the ribonucleoprotein complex telomerase (30-32). Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPS cells) express high levels of telomerase (33-34). However, progressive differentiation is associated with a decrease in telomerase expression and the activity (35-38). Therefore, high levels of telomerase and long telomeres are observed in ESCs, and low levels of telomerase and shorter telomeres are observed in more differentiated cells. Differentiation-induced telomerase repression occurs through multiple pathways, including chromatin modification of the genes encoding the various components of telomerase (38). Therefore, most human adult somatic cells either lack telomerase activity completely or have levels insufficient to overcome the Hayflick limit (39). The importance of telomerase in prolonged proliferation has been demonstrated by ectopic over-expression of the telomerase catalytic subunit (TERT), which enables somatic telomerase-negative cells to overcome the Hayflick limit (40-42). In comparison, most cancer cells express high levels of telomerase (42). The presence of telomerase activity in approximately 90% of human malignancies (43) and the finding that inhibition of telomerase in cancer cells induces cell senescence and eventually cell death (44) suggest that telomerase could aid in the diagnosis of cancer and provide a potential target for cancer therapies (45).

Telomeres can also be extended by the mechanism termed 'alternative lengthening of telomeres' (ALT) that is independent of telomerase. The ALT mechanism involves replication of telomeric DNA by homologous recombination. Although the precise mechanism of recombination in ALT is not known, current theories include a roll-spread replication mechanism that incorporates the use of circular telomeric DNA, elongation of a telomere end using a sister telomere as a template, and elongation of the 3' end of the telomere within the T-loop configuration (46-48).

4. TELOMERE BINDING PROTEIN COMPLEXES

The nature of the specialised nucleoprotein cap (49-50) that protects the tips of telomeric DNA is not fully understood, however, several telomere binding proteins and complexes have been identified, some of which are unique to telomeres. Changes to the composition of telomere binding proteins, by silencing or over-expression of individual or multiple proteins, alter telomere homeostasis in a way that usually manifests as telomere shortening, lengthening or fusion. The shelterin and Rap-TRF2 complexes are two large telomere-specific multi-protein complexes that were identified in mammalian cells by mass spectrometry (51-53). Both complexes have interchangeable protein components and gain access to double-stranded telomeric DNA by binding either TRF1 or TRF2. The POT1-TPP1 and CST complexes, like telomerase, are single-stranded telomere binding protein complexes.

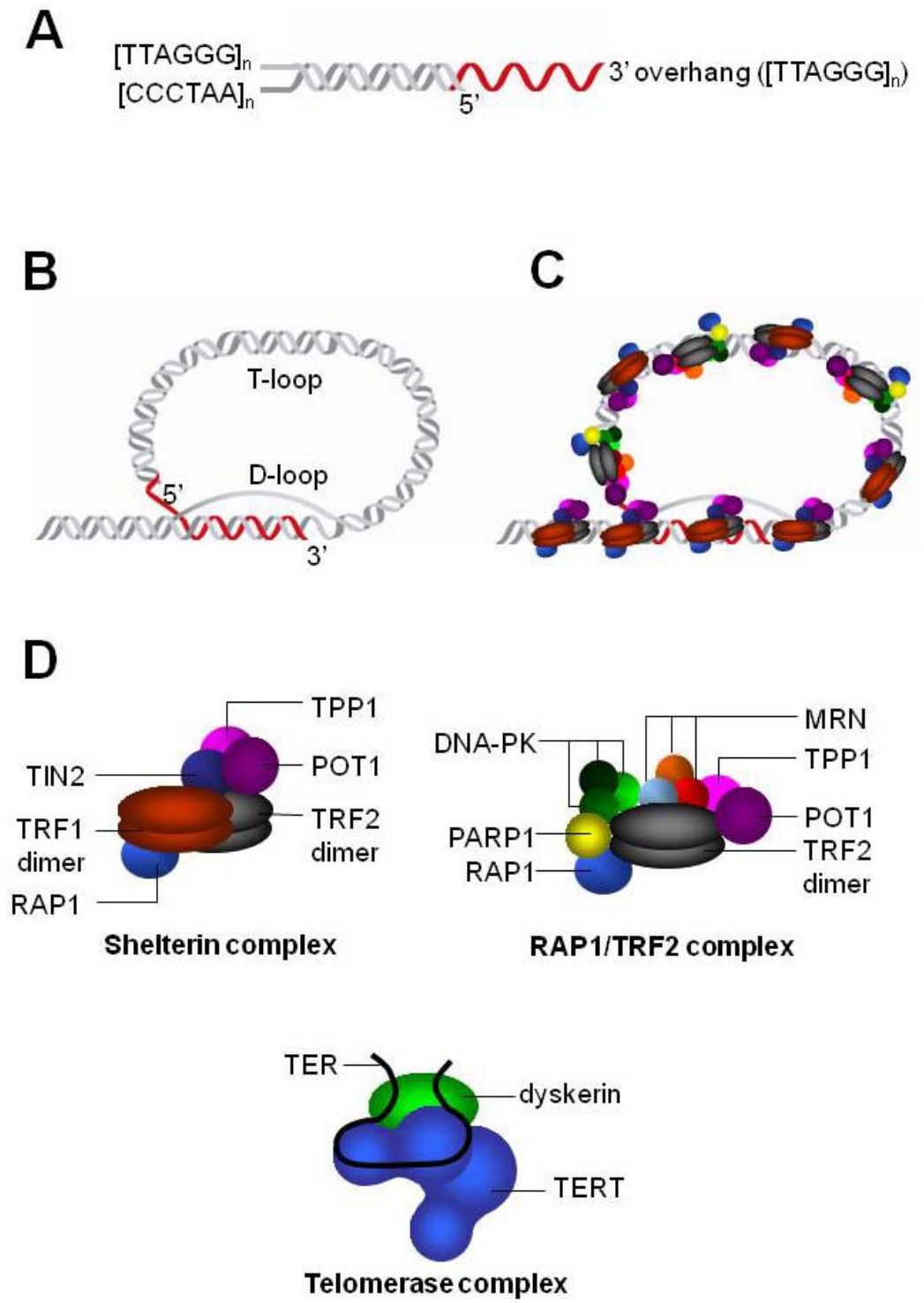

Figure 1. Chief telomere binding protein complexes and configurations of telomeres. (A) Telomere terminus showing single-stranded 3'overhang (red) formed by extension of the G-rich strand of telomeric DNA. The C-rich strand (terminating 5' orientation) exists mainly as double-stranded DNA. (B) The T-loop/D-loop configuration of telomeres. The 3'overhang (red) invades the duplex telomeric DNA to form the D-loop. (C) Coating of telomeres by the shelterin and RAP1/TRF2 complexes (see text for discussion) to form the telomere terminal cap. Although two protein complexes are shown, it is believed a diverse range of proteins contribute to cap telomeres. (D) Composition of the shelterin, RAP1/TRF2 and telomerase complexes. Only core catalytic components of telomerase are shown.

4.1. Telomerase complexes

The telomerase complex, with a molecular mass between 650 and 670 kD (54), is a specialised reverse transcriptase comprised of a catalytic core and several associated proteins. The catalytic core of human telomerase contains the catalytic subunit TERT, a 1132-amino acid residue reverse transcriptase; the 451-nt RNA moiety TER; and the TER binding protein dyskerin, a 514-amino acid residue protein (54). In addition to the catalytic core, the telomerase complex includes several other telomerase binding proteins, such as the ATPases pontin and reptin (55), the TER binding proteins Garl1, Nop10 and NHP2 (56), telomerase Cajal body protein 1 (TCAB1) (57), and heat shock proteins hsp90 and p23 (58-59). Although TER and dyskerin are expressed ubiquitously in normal and cancer cells (60-65), TERT is specifically present in highly proliferative or cancerous cells (65-67) and subject to positive and negative regulation by opposing cellular factors (reviewed in (68)).

TER and TERT are both regulated by alternative splicing which may alter telomerase-telomere complexes. TER exists in multiple forms including the short mature functional form and the immature longer TER RNA precursor that contains multiple polyadenylation sites and poly (A) tails of variable length (69). The findings in budding yeast that inhibition of TER splicing generates inactive forms of telomerase and causes progressive telomere shortening suggest that TER splicing is an important regulatory step in the biogenesis of functional yeast telomerase (69). Various forms of TERT arise from alternative splicing of TERT mRNA (70). Such telomerase complexes may exist in different forms with or without altered levels of telomerase activity. Ectopic expression of wild type TERT in telomerase-negative cells is sufficient to generate telomerase activity and extend cell lifespan, demonstrating that TERT is the rate-limiting component of telomerase (41). Therefore, the fate of telomerase largely depends on the presence and/or biological activity of both TER and TERT. Many strategies to regulate telomerase, such as in cancer therapies, target the expression or activity of TERT or TER.

To initiate reverse transcription, telomerase recognises, binds and orientates the 3'-overhang of telomeric DNA into its active site. TERT then copies the TER template one nucleotide at a time, until it reaches the 5′-boundary of the template region (71), where TERT undergoes a translocation to the newly formed telomere 3'-end for reverse transcription of another telomeric DNA repeat. TERT contains DNA-binding regions known as anchor sites upstream of the RNA-DNA hybrid to stabilise TERT binding to telomere (71). The actions of telomerase in stabilising and elongating telomeres are regulated by other telomere binding protein complexes, including shelterin (see below). Telomerase assembly and stabilisation, recruitment to telomeres, and reverse transcription activity and processivity at telomeres are regulated by telomere binding proteins.

The RNA moieties at telomeres are also implicated in regulating telomerase holoenzyme assembly and activity. These include TER and TER-binding protein complexes that facilitate telomerase complex formation and telomeric repeat-containing RNA (TERRA). TERRA is transcribed from the C-rich strand of sub-telomeric DNA by DNA-dependent RNA polymerase II (72-73) and is localised to telomeres. It inhibits telomerase activity, perhaps by mimicking the substrate nucleotide sequence of TER and thereby competing with TER interaction with its substrate (73). Consistent with the telomerase inhibitory function of TERRA, reduced levels have been associated with increased cytosine methylation in the sub-telomere region of telomerase-positive cells, suggesting that methylation silences TERRA transcription to allow telomerase-mediated maintenance of telomeres (74).

Recently, studies have demonstrated that telomerase holoenzyme assembly is dependent on the AAA+ family ATPases pontin and reptin that shuttle between TER and TERT to form two sub-complexes (55). Pontin and reptin are essential for the structural integrity and catalytic activity of several chromatin remodelling complexes. Pontin-reptin complex interacts with TERT during S-phase of the cell cycle, but is not required for telomerase activity, suggesting that the ATPases are primarily involved in telomerase assembly (55).

Since telomerase has been shown to exert its function in addition to telomere length maintenance (75-76), studies have been carried out to investigate possible interactions of TERT with proteins not associated with telomere maintenance (see below). In addition, effects observed following telomerase activation and inactivation may not result from changes in telomere length or stabilization, but also from the telomere position effect (TPE) impacting on gene expression (77). The telomere-independent effects of TERT might thus involve TERT forming a complex with other transcription regulatory molecules or TER interactions with proteins other than TERT (see below).

4.1.1. TERT sub-complexes

It has been demonstrated that telomerase cellular function can be independent of telomerase maintenance of telomeres (78). Expression of telomerase inhibits the anti-proliferative effect of TGF-β (79). Whereas inhibition of TERT increases the susceptibility of cells to apoptosis, expressing catalytically inactive TERT mutants enhances the survival of cells (80-82). Investigating the apparent telomere maintenance-independent function of TERT, recent studies have shown that TERT forms a complex with certain gene promoters, such as mouse and human beta-catenin (83). In human cancer and mouse ES cells, TERT forms a complex with BRG1 (Brahma-related gene 1 or called SMARCA4 (83). BRG1 is an ATPase subunit of the SWI/SNF chromatin remodeling enzymes that disrupt histone-DNA contacts), and activates Wnt-dependent reporters for beta-catenin gene transcription (83). The SWI/SNF (switch/sucrose non-fermentable) complex regulates gene expression by altering chromatin structures during epigenetic regulation (84). Interestingly, BRG1, complexed with $p54^{nrb}$ (a DBHS (Drosophila behaviour, human splicing) family protein), has already been shown to

be involved in *TERT* gene transcription and splicing of the *TERT* transcript in human tumor cells (85). Thus, a positive regulation may exist for BRG1 to regulate not only the *TERT* gene but also TERT gene transcriptional action. BRG1-p54^{nrb} complex up regulates *TERT* (85), and subsequently, BRG1-TERT up regulates *beta-catenin* (83).

The switching mechanisms in controlling BRG1 interactions with the *TERT* gene or TERT protein are unknown. In human HeLa cells, BRG1 co-purified with TERT, and in mouse ES cells, TERT binds BRG1 in both co-immunoprecipitation and GST fusion pull-down assays (83). The mechanism of TERT stimulating the beta-catenin gene transcription independently of telomeres was demonstrated by chromatin immunoprecipitation of the endogenous TERT with gene promoters of Wnt-dependent genes (83). Additional evidence for the direct participation of TERT in Wnt/beta-catenin signalling, through the role of TERT as a cofactor in a beta-catenin transcriptional complex, comes from studies showing TERT to be essential for both the formation of the anterior–posterior axis in Xenopus laevis embryos, and homeotic transformations in the vertebrae of Tert2/2 mice with Wnt signalling defects (83). However, recent studies have also shown that lack of either TERT or TER has no effect on differential gene expression in mice (86).

In addition, studies have shown that TERT is recruited to promyelocytic leukaemia (PML) nuclear bodies through its interaction with PML-IV (87). In the H1299 human lung carcinoma cell line, the binding is mediated by interactions between the PML-IV C-terminal region (residues 553-633) and two regions of TERT (residues 1-350 and 595-946) (87). The inhibition of telomerase activity by PML-IV occurs in HEK293T, U2OS and HTT cell lines, and is mimicked by the amino acid 553-633 fragment of PML-IV but not other PML isomers in H1299 cells (87). These findings are consistent with PML-induced premature senescence and up-regulation of p53 (88). Furthermore, treatment of H1299 cells with interferon-alpha (IFN-alpha) results in increased levels of PML proteins and a concurrent decrease in telomerase activity (89-90). IFN-alpha induces the localisation of exogenous TERT to PML nuclear bodies and increases the binding between TERT and PML, whereas depletion of PML reverses IFN-alpha-induced telomerase inhibition (87). These results suggest that PML-IV forms a complex with telomerase to regulate compartmentalisation and availability of TERT.

It is fundamental to address if TERT forms complexes with other protein(s) at telomeres, particularly with proteins that regulate or inhibit TERT telomere lengthening activity. Human Pif1 binds telomeres and also TERT (91-92). Consistent with yeast Pif1 that inhibits telomerase catalytic activity (93) and removes telomerase off the telomeres (94), human Pif1 inhibits telomerase processivity resulting in telomere shortening in fibrosarcoma HT1080 cells (92). Moreover, Pif1 inhibition of telomerase activity has been suggested to be mediated by Pif1 helicase activity in unwinding the DNA/RNA duplex formed by telomerase RNA TER and telomeric DNA (92), consistent with the removal activity of telomerase from telomeres in yeast (94). However, although Pif1 is detected in mouse embryonic and hematopoietic lineages, knockout of Pif1 in mice results in viable and apparently healthy animals without affecting telomere maintenance and telomerase activity (95).

Furthermore, the house-keeping glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) undergoes nuclear translocation in response to cellular stress (96-97) and binding to telomere (98-99). Studies in our laboratory found recently that GAPDH binds TERT and inhibits telomerase activity, suggesting a novel mechanism mediating stress-induced telomere shortening (unpublished data). Further studies are required to define the switching mechanisms of TERT in the different complexes of telomerase containing TER, the gene transcription co-factor complex containing BRG1, the TERT PML complex containing PML-IV, TERT-Pif1 and TERT-GAPDH complexes. Such switching requires regulation not only of TERT trafficking and interaction with different recruiting molecules, but also of the availability of TERT binding partners (such as BRG1, PML-IV and GAPDH).

4.1.2. TER sub-complexes

Human TER is related to box H/ACA small ribonucleoprotein particles (RNPs) (100-102) of which there are at least two functional complexes. First, the box H/ACA small nucleolar (sno)RNPs that accumulate in the nucleolus and direct the modification of rRNAs and spliceosomal U6 snRNA; second, the box H/ACA small Cajal body-specific (sca)RNPs that accumulate within Cajal bodies and are involved in the modification of the nucleotides of spliceosomal snRNAs transcribed by RNA polymerase II (103-104). Human TER features at its 3′-end conserved H- and ACA-boxes involved in RNA splicing (105), and a CAB-box involved in the retention of scaRNPs within Cajal bodies (106) where TER accumulates in a cell cycle dependent manner (57, 102, 107-108). It appears that the integrity of the TER H-box or the ACA-box is required for normal biogenesis and accumulation of TER (100). Similar to other H/ACA RNAs, TER binds the four conserved proteins dyskerin, hGar1, hNhp2, and hNop10 to form the snoRNPs and scaRNPs (109-110). In addition, the interaction of TER with hNaf1 is required for telomerase assembly (111). It is not known how dyskerin, hGar1, hNhp2, hNop10 and hNaf1 are assembled with TER. However, silencing of TCAB1, a protein enriched in Cajal bodies that interacts TER and other scaRNAs, disrupts the association of TERC with Cajal bodies and telomere elongation by telomerase. This suggests that TCAB1 recruits TER to Cajal bodies playing a role in telomerase assembly and activity (57).

4.2. The shelterin complex

The shelterin complex, also known as the telosome, is a unique multi-protein telomere-specific interactome that maintains telomere structure and caps telomere ends (51, 112). The protein complex is made up of six proteins that bind both single- and double-stranded telomeric DNA to regulate telomere maintenance. They are

TRF1, TRF2, POT1, TIN2, TPP1 and RAP1, which collectively contribute to normal telomere function. The core components of the shelterin complex are TRF1 and TRF2, which bind double-stranded telomeric DNA repeats in mammals. TRF1 and TRF2 form homodimers by an N-terminal homodimerization domain and bind strongly to duplex telomeric DNA through Myb-type DNA-binding domains called teloboxes (113-114). In doing so, TRF1 and TRF2 provide access points by which a range of proteins can interact with telomeres indirectly.

TRF1 is essential for telomere capping and regulation of telomere length and also serves as a critical factor in efficient replication of telomeric DNA (115). Whereas over expression of TRF1 results in telomere shortening (116-119), depletion of TRF1 results in rapid induction of the telomere damage response and cell senescence in an ATM/ATR-dependent manner (120). Over-expression of TRF1 in transgenic mice also results in increased telomere damage foci, end-to-end chromosomal fusions and telomere recombination (121). TRF1 binding is proportional to telomere length (118), and is believed to form a negative feed-back loop to restrict elongation of long telomeres by telomerase.

In contrast, TRF2 is critical for defining the ends of the chromosome as telomeres. Inhibition of TRF2 results in the detection of telomeres as DNA breaks, causing telomere fusions and eventually cell death or senescence (118, 122-123). TRF2 is believed to protect telomeres by aiding the formation of T-loops (18, 124) and direct suppression of DNA damage responses. It has been proposed that TRF2 interacts with Chk2, an ATM/ATR pathway effector kinase, to suppress its activation in the absence of DNA damage (125). In addition, TRF2 associates at telomeric and non-telomeric genomic double-strand breaks within 2 seconds following DNA damage insults, even in the absence of other key DNA-repair proteins (126).

POT1 and TPP1 each possess an oligonucleotide/oligosaccharide binding (OB) fold that facilitates single-stranded DNA binding (127-129). However, despite having an OB fold, TPP1 does not interact with telomeric DNA directly (128), whereas POT1 specifically binds TTAGGGTTA motifs (130-131). POT1 and TPP1 are involved in modulating telomerase activity (128, 132). Inhibition of both proteins by shRNA leads to telomere elongation (53). Inhibition of either POT1 or TPP1 alone leads to a potent DNA damage response at telomeres, caused by disruption of POT1-TPP1 complex at the telomere overhang (133-135).

To fulfil the functions of the single human POT1 gene, mice have two gene isoforms – POT1a and POT1b. Deletion of POT1a results in an increase in telomere length and ATR dependent DNA damage response (136-137). Deletion of POT1b results in large 3'overhangs (136) and an ageing phenotype that manifest as a dyskeratosis congenita-like syndrome including hyper-pigmentation and fatal bone marrow failure (138). These findings suggest that telomere capping by POT1 is critical for prevention of an ageing phenotype (134). However, more recent studies have shown that TPP1 is required for POT1a and POT1b binding to telomeres, since deletion of TPP1 in mouse embryo fibroblasts results in telomere dysfunction identical to that induced by double gene disruption of POT1a and POT1b (135).

TRF1-interacting nuclear protein 2 (TIN2) links the POT1-TPP1 heterodimer and the TRF1-TRF2 double-stranded DNA binding complexes (Figure 1) (51, 139-140). The stable interaction also bridges TRF 1 and TRF2 homodimers that otherwise do not interact (51, 112, 140-141). Knockout of the mouse TIN2 gene results in early embryonic lethality highlighting its importance to telomere function (142). In addition, a significant number of human patients with dyskeratosis congenita have mutations in the TIN2 gene (143-144).

RAP1 (repressor activator protein 1) has been identified as a component of the shelterin complex that is also often mutated in human dyskeratosis congenita patients. Human RAP1 has a single Myb-homology domain, but appears not to bind telomeric DNA directly (145). RAP1 interacts with TRF2 to form a distinct complex (see below). Although the precise role of RAP1 is unknown, knockdown of RAP1 expression by shRNA results in telomere lengthening (52), suggesting that RAP1 is a negative regulator of telomere length maintenance.

Quantitative immunoblotting to determine the stoichiometry of shelterin proteins in the protein bound fraction of DNA has yielded clues to additional roles of shelterin components. Interestingly, the TPP1-POT1 heterodimer is in excess of its single-stranded telomeric DNA binding sites, suggesting that the complex might associate with non-telomeric DNA (146). Whereas TRF2 and Rap1 are present at 1:1 ratio, as are TPP1 and POT1, TIN2 is 10 fold less abundant than TPP1 and POT1. The discovery of more abundant RAP1 and TIN2 than previously thought indicates as yet unidentified roles of RAP1 and TIN2 in telomere maintenance or telomere-independent functions (12). In addition, sufficient TRF1 and TRF2 is present to allow binding of all telomeric DNA in cells with short telomeres and similar results were obtained for primary and transformed human cells, with short and long telomeres respectively, suggesting that there is no relation between protein proportions and telomere length (146).

4.3. The CST complex

Originally identified in yeast, the CST telomere binding protein complex caps telomeres and protects them from lethal DNA degradation. In yeast the complex is comprised of Cdc13 and the Stn1-Ten1 heterodimer that Cdc13 binds weakly (147-149) (Figure 2). In humans (and other organisms), the CST complex contains conserved telomere maintenance component 1 (CTC1) and mammalian STN1 and TEN1 homologs (150-151). The CST proteins contain multiple putative OB-folds and the complex binds to single-stranded DNA with high affinity in a sequence-independent manner (150). Knockdown of CTC1 or STN triggers increased single-stranded G-strand

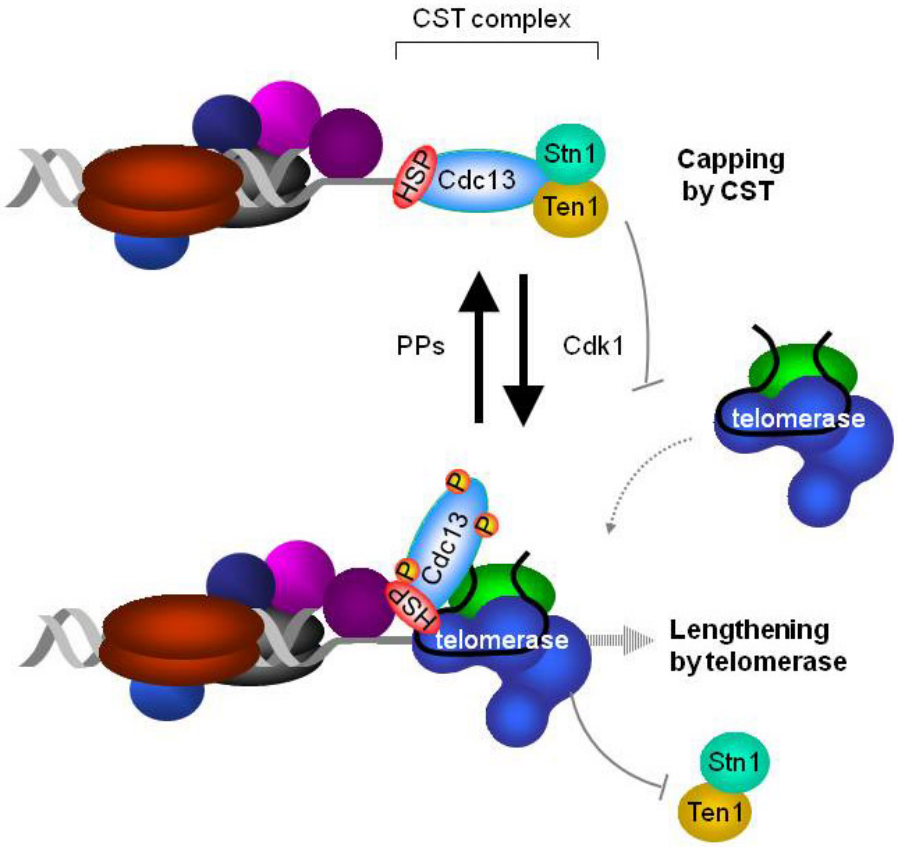

Figure 2. Bimodal function of Cdc13 in telomere capping and telomere elongation. Cdc13 binds Stn1 and Ten1 to form the CST complex and cap single-stranded telomere tips, thereby preventing docking and extension of telomeres by telomerase (top). Stn1 and Ten1 dissociation upon Cdc13 phosphorylation enables telomerase to dock at telomere termini through interactions with Cdc13 and elongate telomeres. Hsp 82 (HSP) is required to mediate the transition between the telomere capping and elongation function of Cdc13. Cdc13 phosphorylation is mediated by Cdk1 and dephosphorylation by protein phosphatases (PPs) of Cdc13 to enable Stn1/Ten1 binding and telomere capping. It is unknown if other telomere associated kinases, such as ATM/ATR and DNA-PK, can phosphorylate Cdc13 to regulate telomerase docking or if Cdc13 is required for telomere elongation following docking of telomerase.

overhangs and telomere loss (150-151). Structural studies suggest that the Stn1-Ten1 heterodimer is a conserved replication protein A (RPA)-like telomeric complex that may operate in parallel with the POT1-TPP1 dimer at 3' overhangs (152-153). Indeed, it was recently reported that OBFC1/AAF44, the human homolog of yeast Stn1, binds single-stranded telomeric DNA and associates with TPP1 to regulate telomere length (154). Mutation of OBFC1/AAF44 leads to telomere elongation in human cells, suggesting an important role in telomere length regulation (154).

4.4. The RAP1-TRF2 complex

RAP1 is part of another telomere binding complex that includes TRF2, Rad50, MRE11, Ku70, Ku80, and PARP1 (52) (Figure 3). MRE11 and RAD50 are also components of the MRN complex that bind DNA, whereas Ku70 and Ku80 are components of the DNA-PK complex (see below). MRE11, RAD50 and Ku70/80 perform an important role in telomere homeostasis by capping telomeres and also regulating telomere maintenance. The poly(ADP)-ribosylase PARP1 binds and modifies TRF2, affecting its DNA binding (155-156). Similarly, other poly(ADP)-ribosylating enzymes, such as PARP2, and Tankyrases 1 and 2, are important for telomere integrity and maintenance (155, 157-160). However, the mechanisms by which these proteins contribute to telomere homeostasis are unclear. Silencing PARP1 results in telomere shortening without altering telomerase activity, and the release of cells from PARP1 inhibition leads to the rapid regeneration of telomeres (161).

4.5. The MRN complex

The MRN complex, comprised of MRE11, RAD50 and NBS1, is required for maintenance of telomere length in mammals, plants and yeast (162). It is involved in all activities responsible for telomere integrity, including DNA repair, telomere capping and telomere lengthening. Although MRE11 and RAD50 bind DNA directly, NBS1 binds indirectly through MRE11, stabilising the interaction between MRN and DNA (163). The MRN complex may be involved in four functions: telomere capping, generation of

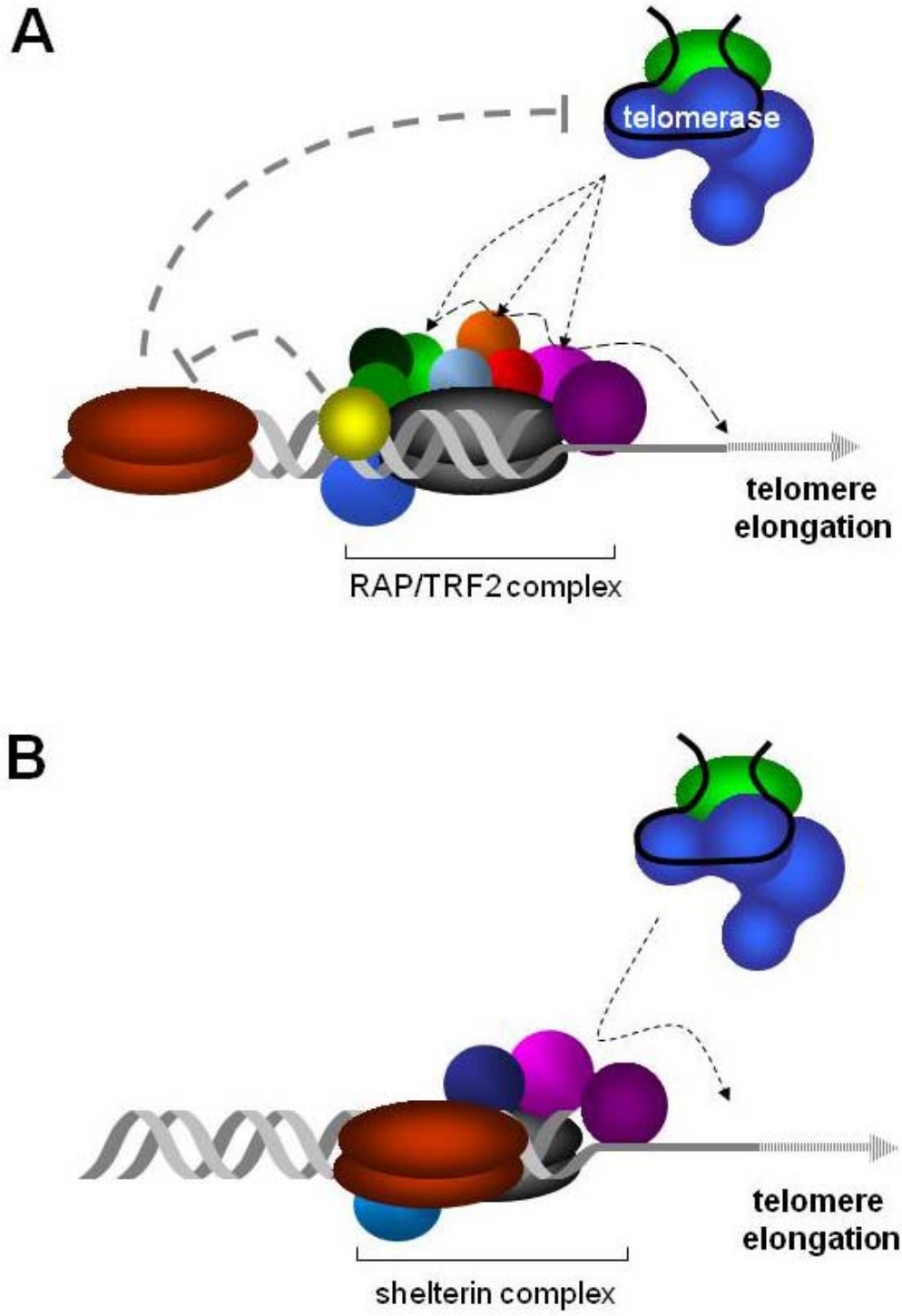

Figure 3. Models for telomerase recruitment by telomere binding complexes. (A) The RAP/TRF2 complex (comprising RAP1, TRF2, PARP1, the DNA-PK complex, MRN complex, TPP1 and POT1) has three elements that can directly interact with telomerase –TPP1, MRN complex and DNA-PK complex. These components might serve to attract telomerase to the RAP/TRF2 complex and bring telomerase close to telomere tips. The RAP/TRF2 complex also comprises elements (e.g. PARP1) that can modify *cis*-inhibitory elements of telomeres such as TRF1. Therefore, through a number of mechanisms, the RAP/TRF2 complex may assist recruitment of telomerase. (B) The shelterin complex (comprising TRF1, TRF2, RAP1, TIN2, TPP1 and POT1) may also recruit telomerase through TPP1. However, shelterin may also participate in TRF1 mediated *cis*-inhibition of telomerase.

the 3'-G rich overhangs, regulation of telomerase, and triggering telomeric DNA damage responses. The possible telomere capping role of MRN is supported by observations that NBS1-deficient cells have shorter telomeres (164) and cells expressing mutant NBS1 have unstable telomeres (165). Furthermore, NBS1 interacts with TRF2 during S-phase (166) and although the precise role of the MRN/TRF2 interaction is unclear, it may be related to T-loop formation.

The capping function of MRN is particularly important for protecting 3'overhangs after DNA synthesis in the G2 phase of the cell cycle (167). Gene silencing to reduce MRN results in a transient shortening of the 3' overhang in telomerase-positive cells (168). When telomeres are critically short, MRN is also involved in initiating telomeric DNA damage responses. MRE11 can directly activate ATM in response to DNA double-strand breaks (DSBs), triggering ATM-dependent DNA damage responses (169). MRN accumulates at damaged telomeres with 53BP1, γ-H2AX and phosphorylated ATM to form telomere dysfunction-induced foci (TIF) (140, 170-171). Recent data show that MRN contributes to telomere fusions arising from TRF2 deficiency in G1 phase of the cell cycle (167), and NBS1 is critical for activation of the ATM pathway in response to telomere dysfunction (167, 172). The nuclease activity of NBS1 is also important for the induction of telomere-chromosomal fusion (172). Consistently, MRN nuclease deficiency is required for MRN induction of ATM after DNA damage (173). Therefore, MRN is a multifaceted protein complex able to protect telomeres and elicit DNA damage response.

4.6. The DNA-PK complex

DNA-dependent protein kinase (DNA-PK) is composed of three subunits, Ku70, Ku80, and the catalytic component DNA-PKcs (DNA-dependent protein kinase catalytic subunit). With DNA ligase IV, Artemis and XRCC4, DNA-PK is a core component of the mammalian non-homologous end joining (NHEJ) machinery (174). DNA-PK interacts directly with telomeric DNA in yeast (175) and indirectly in mammals through interactions with TRF1 and TRF2 (176-177). In human cells, DNA-PK interacts with telomerase directly by binding TERT through Ku70 and Ku80 (178). DNA-PK is involved in telomere capping and telomerase regulation. Consistent with the telomere capping function of DNA-PK, Ku80-deficient mouse primary cells show increased telomere fusions and long telomeres (176, 179). In addition, Ku70 and TRF2 are required for repression of exchanges between sister telomeres (180). Therefore, DNA-PK contributes to telomere capping and prevents homologous recombination of telomeres.

4.7. Other telomere protein complexes

In addition to the multiprotein complexes described above, numerous other telomere binding proteins that are important for telomere maintenance and integrity have been identified in mammalian cells. These include Rad51D (181), Apollo (182-184), GNL3L (185), WRN and BLM helicases (186-190), and ERCC/XPF (191-193) (Table 1). Many of these proteins (Apollo, GNL3L, WRN, BLM and ERCC/XPF) interact with, and modulate the activities of TRF1 or TRF2. In addition, BLM in concert with TRF1 has been identified as necessary for efficient replication of TTAGGG-bearing telomeric DNA and prevention of replication fork stalling during S-phase (115). However, how these proteins interact with other telomere binding complexes, if they do at all, is yet to be fully understood.

5. INTERACTIONS BETWEEN TELOMERASE AND TELOMERE BINDING COMPLEXES

Telomere binding proteins serve as gate keepers that regulate the access of telomerase to its substrate. They limit access either by direct *cis*-inhibition of telomerase at telomeres, or by modulating telomeric chromatin into configurations that deny telomerase access. It is thought that two telomeric configurations regulate the access of telomerase to telomeres. One is the 'open' configuration in which the D-loop is unlocked and the T-loop is open, presenting the 3'overhang for telomere elongation by telomerase. The second, 'closed' configuration involves an intact D-loop that conceals the 3'overhang, thereby limiting access of telomerase to telomeres. It is not known how the structure of telomeres switches between the open and closed configurations. Even in the "open" form, the 3' overhang may still be unavailable as a substrate for telomerase elongation due to the presence of single-stranded telomere binding protein complexes that conceal telomere termini and regulate telomerase recruitment through protein complex interactions.

5.1. Interactions between telomerase and shelterin complexes

Whereas TRF2 plays an important role in formation of the T-loop (124, 194-195), TRF1 is involved in *cis*-inhibition of telomerase. TRF1 over-expression leads to telomere shortening (118-119), and dominant negative TRF1 leads to telomere elongation (119), except in ALT cells, suggesting that TRF1 mutation-induced telomere lengthening depends on telomerase (117). Furthermore, direct tethering of TRF1 to the telomeres of specific chromosomes leads to shortening of those telomeres, confirming a *cis* inhibitory effect on telomere lengthening (116). Since TRF1 binding to telomeres is proportional to telomere length (118, 131), *cis*-inhibition of telomerase by TRF1 may have evolved to give shorter telomeres priority for elongation. TRF1 might achieve *cis*-inhibition by mechanisms that include the recruitment of proteins that inhibit telomerase directly or modify telomere conformation. Depletion or mutation of TRF1's shelterin partners, POT1, TIN2 and RAP1, results in lengthening of telomeres, implicating the shelterin complex in preventing access of telomerase to telomeres (52, 112, 132).

However, POT1 can have a dual role in regulating telomerase. Purified recombinant POT1 binds telomeric DNA and inhibits telomerase activity *in vitro*, possibly by sequestering the telomere ends (196). Conversely, POT1 enhances telomerase processivity by binding to telomeric DNA and presenting telomerase a single strand substrate of 8 nucleotides for telomere

Table 1. Mammalian telomere binding proteins and their functions

Protein	Notes/Functions	Direct DNA-binding	Direct Interaction partners	Ref
Apollo	DNA exonuclease Telomere capping	no	TRF2, RAP1	(183)
BLM	DNA helicase Unwind TRF2 bound telomeric DNA	yes	TRF2, TRF1	(186-187)
CST complex	Positive and negative telomere length regulator	yes	TPP1, telomerase	(150-152)
DNA-PK complex	Prevention of NHEJ of telomeres Telomere capping	yes	TRF1, TRF2, telomerase	(180)
ERCC1/XPF	Nucleotide excision repair endonuclease Double minute chromosome prevention Responsible for causing partial 3'-overhang loss and telomere shortening due to TRF2 depletion	yes	TRF2	(191)
GNL3L	Promotes TRF1 homodimerization Associates with telomerase	unknown	TRF1, telomerase	(185, 221)
MRN complex	Telomere capping DNA damage sentinel Telomerase recruitment ALT telomere maintenance	yes	TRF2	(166)
PARP1/2	Poly(ADP-ribosyl)ases Positive telomere length regulator DNA damage repair	no	TRF2, RAD50, MRN, DNA-PK, RAP1	(52)
PINX1	Negative regulator of telomere length Telomerase inhibitor in vivo and in vitro	no	TRF1, telomerase	(201)
POT1	Binds single-stranded TTAGGG repeats	yes	TPP1, TRF2	(127)
RAD51D	Telomere capping	unknown	unknown	(181)
RAP1	Binds TRF2 Important in blocking NHEJ of telomeres Telomere capping	no	TRF2, MRN, PARP1, DNA-PK	(145)
Tankyrase 1/2	Poly(ADP-ribosyl)ases Positive telomere length regulator	no	TRF1, TIN2	(112, 157)
Telomerase complex	Lengthens telomeres Telomere capping	yes	TPP1, PINX1	(128) (129) (201)
TIN2	Binds TRF1, TRF2 and TPP1 in shelterin	no	TRF1, TRF2, TPP1	(139)
TPP1	Binds, POT1, TIN1. Directly interacts with telomerase	no	POT1, TIN2, telomerase	(129)
TRF1	Negative regulator of telomere length (telomerase dependent) Telomere capping protein Binds double-stranded TTAGGG repeats	yes	TIN2, PINX1, DNA-PK	(113, 222)
TRF2	Binds double-stranded TTAGGG repeats Knock down causes telomere fusion Telomere capping protein Required for T-loop formation	yes	TIN2, WRN, BLM, DNA-PK, MRN	(114, 223)
WRN	DNA helicase Unwind TRF2 bound telomeric DNA	yes	TRF2	(190)

elongation (197). When POT1 associates with TPP1 on single-stranded telomeric DNA, the heterodimer protects telomeres by capping and elongates telomeres by recruiting telomerase (128-129) (Figure 3). POT1 binds telomeric DNA with increased affinity and enhances telomerase processivity when bound to TPP1, which directly interacts with TERT *in vitro* in a TPP1 OB-fold dependent manner (128-129). Thus, the regulation of telomerase activity by POT1 depends on interactions with other proteins on double- and single-stranded telomeric DNA.

These observations demonstrate the critical role of TPP1 in recruiting telomerase to telomeres in a POT1 dependent manner (129). A hypomorphic mutation in the mouse TPP1 alleles is associated with telomere capping defects leading to adrenal gland dysplasia, male germ cell loss and skin hyperpigmentation (198). Moreover, mice lacking both p53 and TPP1 function are predisposed to rapid development of cancer and a shift from sarcomas and lymphomas to dominant carcinomas (including skin carcinoma and adrenocortical carcinoma) (198). The similarity in phenotype of mice with double deficiencies in TPP1 and p53, and telomerase TERC and p53 (199), is consistent with the TPP1/POT1 function in recruiting telomerase to telomeres.

POT1 has also been shown to interact with the nuclear protein PINX1, which may regulate the recruitment of telomerase onto telomeres by TPP1/POT1 (200). PINX1 binds both TERT and telomeric DNA and inhibits telomerase activity directly (201). Genetic ablation of PINX1 expression in yeast cells results in shortened telomeres (202). Knock down of constitutive PINX1 expression in telomerase-positive human cancer cells *in vitro* and xenograft tumours in mice also leads to telomere shortening and growth inhibition, apparently due to decreased association of telomerase with the POT1-containing telomeric protein complex (200). Therefore, PINX1 is required for telomerase recruitment and telomere maintenance in telomerase-positive cancer cells.

5.2. Interactions between telomerase and CST complexes

In budding yeast, Cdc13 binds either Stn1-Ten1 or Est1 (telomerase), in order to form operative complexes that caps or extends single-stranded G-rich telomeric DNA

(203). The C-terminal region of Cdc13 mediates the Stn1-Ten1 interaction and the N-terminal region mediates the telomerase interaction with telomeres (204). The telomere capping and extending activities of Cdc13 are modulated by the yeast Hsp90 chaperone Hsp82, which promotes the transition of Cdc13 between the two complexes (204).

Protein phosphorylation is a key mechanism that determines Cdc13 association with Stn1-Ten1 and telomerase in yeast (205-207) (Figure 2). Tseng et al (205) showed by an immunoprecipitation-kinase assay that Mec1 and Tel1 (yeast ATR/ATM) phosphorylate Cdc13 SQ/TQ motifs *in vitro*. Cdc13 is phosphorylated by Mec1 on serine 225, 249 and 255, and 306, whereas Tel1 phosphorylates serine 225, 249 and 255. In addition, mutation of these phosphorylation sites induces multiple telomeric and growth defects in yeast. The finding that normal telomere length and growth could be restored by the expression of a Cdc13-Est1 fusion protein, demonstrates that phosphorylation of SQ/TQ motifs by Mec1/Tel1 within the telomerase recruitment domain of Cdc13, is important for recruiting telomerase to telomeres (205). It has also been demonstrated in yeast that Cdk1-dependent phosphorylation of Cdc13 promotes the interaction of Cdc13 with Est1 to extend telomeric DNA (206-207). Cdk1 phosphorylates S/TP motifs on residues 308 and 336 of Cdc13 and mutation of these sites induces telomere shortening, cell cycle arrest and alters normal Cdc13 protein turnover (207). These findings suggest that Cdk1 phosphorylates the telomerase recruitment domain of Cdc13 facilitating telomere replication and cell cycle progression in addition to maintaining optimal Cdc13 protein levels during the cell cycle (207). Therefore phosphorylation of Cdc13 by Cdk1, Mec1 and/or Tel1 in yeast is important for telomerase dependent DNA extension events (Figure 2).

The functional interaction between Cdc13 and telomerase in yeast resembles that of POT1 and telomerase in humans (208). When bound near the 3'overhang of telomeric DNA, both the full-length Cdc13 and its DNA-binding domain competitively block access of telomerase to its substrate in vitro (208). However, Cdc13 also shows a novel 'action at a distance' inhibitory activity when the 3'overhang is present in excess (208). Thus, Cdc13 recruits telomerase to telomeres in a switched 'off' mode. Further investigation is needed to determine whether the switch is turned 'on' by Cdc13 phosphorylation or by a similar signal that regulates the POT1-TPP1 complex in mammalian cells. It has also been suggested that Stn1 inhibits telomerase at an early stage by recruiting the Pol a-primase to polymerise the C-strand of telomeres in yeast (206, 209-210).

5.3. Interactions between telomerase and DNA-PK complexes

In mammalian cells, DNA-PK is suggested to be involved in both telomerase recruitment and telomere capping. The Ku70/80 dimer of the DNA-PK complex interacts directly with TERT in human cells. Antibodies against human Ku proteins precipitate telomerase from cell extracts of tumour and telomerase-immortalised normal cells, and also in vitro reconstituted telomerase, suggesting direct protein-protein interaction (178). Consistently, Ku is associated with in vitro translated TERT in the absence of TER or telomeric DNA (178). Furthermore, deletion of both TER and DNA-PKcs in mice increases the rate of telomere shortening compared with the deletion of TER alone, suggesting a telomerase independent role of DNA-PKcs in the maintenance of telomere length (211). In addition, DNA-PK may interact with telomerase indirectly through the DNA-PK interacting protein KIP (DNA-protein kinase catalytic subunit-interacting protein) that binds TERT in the yeast two-hybrid system, co-immunoprecipitates with TERT from cell-free extracts and co-localises with TERT in the nucleus (212). Over-expression of KIP results in increased telomerase activity and telomere lengthening (212).

Studies by Beattie and colleagues (213) revealed an interaction between telomerase and DNA-PK from a different perspective. By using specific DNA-PK inhibitors they found increased rates of telomere loss due to kinase inhibition. This suggests that the kinase activity of DNA-PK is required for its function at telomeres, possibly by phosphorylating proteins required for maintaining telomere length. The heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) , a known telomere and telomerase binding protein (214), is a direct substrate for DNA-PK, and phosphorylation of hnRNP A1 by DNA-PK is stimulated by both DNA and also TER (213). In human cell lines lacking TER, DNA-PK-dependent phosphorylation of hnRNP A1 is greatly decreased, indicating that TER stimulates the kinase activity of DNA-PK (213). Thus, telomere maintenance in human cells is dependent upon interactions between components of telomerase and DNA-PK , namely between Ku and TERT and between DNA-PKcs and TER.

5.4. Interactions between telomerase and MRN complexes

MRN plays an important role in telomere maintenance by telomerase. In yeast, the intact MRN complex is implicated in preparing single-stranded telomeric DNA for telomerase-dependent extension (215) and recruitment of the telomere replication machinery (including telomerase) at late S-phase (216). Consistently, knock down of MRN by RNAi in yeast, results in transient shortening of the 3' overhang (217). MRN is also important for telomerase independent telomere maintenance that occurs in yeast upon deficiency of the telomere binding protein taz1 and Trt1 (TERT) (218). In addition to the checkpoint kinase Tel1 (ATM) and RAP1, the MRN complex is required for telomere maintenance in taz1/trt1 double-deletion cells. Expression of catalytically inactive Trt1 efficiently inhibits MRN-mediated recombination-based telomere maintenance, suggesting that MRN-Tel1 and Rap1 promote recombination-based telomere maintenance and that this mechanism of maintenance is inhibited by telomerase (218). Thus, MRN is important for telomere maintenance by reverse transcription and homologous recombination, respectively, which enables the survival of yeast when either mechanism is absent.

In mammals, the association of MRN with TRF2 at telomeres during the S-phase targets MRN to telomeres (166, 172). In patients with Nijmegen breakage syndrome, lack of NBS leads to shortened telomeres. Both NBS1 and TERT are needed for telomere elongation in NBS1-deficient fibroblasts (164). Silencing MRN results in a shortening of the 3' overhang in telomerase-positive (but not telomerase-negative) cells, although the terminal nucleotides of both C- and G-rich strands remain unaltered in cells depleted of MRE11 suggesting that MRN is not responsible for specifying the final end-processing event (168). Shortening of the telomere overhang also occurs after the forced expression of exogenous telomerase, suggesting involvement of the MRN complex in the recruitment or action of telomerase (168).

6. PERSPECTIVES

Distinct protein complexes accumulate at telomeric DNA to cap, protect and facilitate lengthening of telomeres. Several complexes of telomere binding proteins interact with telomerase to regulate telomere homeostasis and thus cell fate. Whereas protein complexes that bind double-stranded DNA have a negative role in regulating telomerase, those that bind a single-stranded DNA can cooperate with telomerase to maintain telomeres. Emerging evidence indicates that the processes of capping and lengthening single-stranded telomeres are the function of distinct cellular machinery that includes the POT1-TPP1, CST and telomerase complexes. It is not yet known why there are two interacting telomerase-recruiting single-stranded telomere binding protein complexes. It is possible that the shelterin and DNA-PK complexes perform a house-keeping role on telomere duplexes, while the MRN and telomerase complexes are critical for telomere maintenance in damaged and short telomeres, respectively. Elucidation of the molecular switches that trigger activation and recruitment of the different complexes would provide insight into how telomeres might be reprogrammed and remodelled to achieve desirable effects on cell proliferation potential. In addition, it is not known what changes in telomere binding proteins take place during aging and tumorigenesis. In model systems, the loss of telomere binding proteins generates an aging phenotype, for example mutations of TIN2 and POT1 in dyskeratosis congenita. Whereas a decline of Ku70 and MRE11 expression has been observed with age in the human population (219), loss of telomere binding proteins following repeated antigenic stimulation of lymphocytes has been shown to cause telomere shortening associated with decreased TRF1, TIN2, POT1, RAP1 and TANK1 (220). These observations highlight the necessity for new studies to identify the true contribution of loss of telomere binding proteins to aging-associated telomere loss and cell senescence.

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Abbreviations: DNA-PK, DNA-dependent protein kinase; MRN, MRE11, RAD50 and NBS1; TER, telomerase RNA component; TERT, telomerase reverse transcriptase

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