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Control of Telomeric DNA Replication: Genetics, Molecular Biology, and Physiology

Akira Matsuura and Aiko Matsui

*Graduate School of Advanced Integration Science, Chiba University
Japan*

1. Introduction

Linear chromosome ends are capped with nucleoprotein complexes called telomeres. Telomeres are essential for the integrity of chromosomes, and loss of the capping function caused by telomere shortening or deficiency of a capping protein leads to detrimental consequences, including the formation of abnormal chromosomes, permanent cell cycle arrest (cellular senescence), and cell death (apoptosis). Telomeres are thought to play a major role in preventing normal chromosome ends from being recognized and processed as DNA double-strand breaks (DSBs).

The replication of linear eukaryotic chromosomes suffers from an intrinsic problem called the “end-replication problem”, which in most cells is solved by the specialized enzyme telomerase. However, this telomerase-dependent mechanism is not the only solution to the end-replication problem in eukaryotic cells: a recombination-mediated mechanism has been found to participate in the maintenance of telomeres in several types of cells, including telomerase-defective yeast mutants, some immortalized tumor cells, and embryonic stem cells. Thus, it is now becoming clear that the regulation of telomere replication impacts on development and disease in higher eukaryotes.

In this chapter, we highlight recent topics in telomere biology, notably the regulation of telomere replication and the response to telomere dysfunction. We focus on the molecular regulation of telomere replication during both the mitotic cell cycle and development, and discuss cellular responses to defects in telomere replication and their relationships with human diseases.

2. The early days of telomere research

The physiological importance of the telomere for chromosome maintenance has been known since the 1920s, when the abnormal behavior of chromosomes lacking telomeres was described by two prominent cytogeneticists, Muller and McClintock (Muller, 1938; McClintock, 1941). Meanwhile, the significance of the telomere as a replication machinery of linear chromosomes became clear after the mechanism of DNA replication at the biochemical level was explained, around 1970. That the telomere solves the “end-replication problem” – the inability of the conventional DNA replication machinery to completely copy the ends of linear DNA – was independently proposed by Watson (1972) and Olovnikov (1973). However, the mechanism involved was still elusive at that time.

3. The structure of telomeric DNA

Various models to explain the solution of the end-replication problem in eukaryotic chromosomes were proposed in the 1970s and 1980s, but determination of the structure of the telomere and sequence of telomeric DNA sequence was necessary to determine which model was correct. Using the ciliate *Tetrahymena thermophila*, Blackburn and Gall (1978) found that the terminal portion of minichromosomes consisted of simple, tandem repeats of short DNA sequences (TTGGGG/AACCCC). Later, it was shown that similar sequences, with a signature of tandem repeats containing a cluster of G residues, were commonly found at the chromosomal termini in most eukaryotes.

The functional importance of the repeated sequence was proved in yeast by Szostak and Blackburn (1982). Usually, yeast plasmids replicate in a circular form; linearized plasmids cannot be maintained stably. However, when the terminal repeats of *Tetrahymena* were ligated to each end of a linear yeast plasmid, it was able to replicate in a linear form. This result indicated that the terminal fragments served a conserved function to protect the ends of linear DNA.

The G-rich strand of the telomere repeat is oriented 5' to 3' toward the chromosome terminus. Telomeric DNA consists of a double-stranded region of telomeric repeats, which terminates as a 3' single-stranded overhang called the "G-overhang" (Wright et al., 1997; McElligott & Wellinger, 1997). The conserved nature of telomeric repeats, both as double-stranded DNA and single-stranded G-overhangs, is critical for the recruitment of proteins involved in the formation and function of telomeres.

Because of its specific sequence, telomeric DNA displays unusual properties. Single-stranded G-overhangs have the intrinsic ability to form a specialized structure called the "G-quadruplex" at physiological salt concentrations (Williamson et al., 1989). The G-quadruplex is a four-stranded helical structure composed of stacks of G-quartets that arise from the association of four guanines in a cyclic hydrogen-bonding arrangement. The existence of G-quadruplexes at telomeres has been confirmed *in vivo*, and their functional roles have begun to be explained (Smith et al., 2011).

The G-overhang also contributes to formation of a higher-order structure: the t-loop. The t-loop was first identified by electron microscopic analysis of *in vivo*-cross-linked human telomeric DNA, which was formed by the insertion of the G-overhang into the double-stranded region of telomeric DNA (Griffith et al., 1999). Subsequently, t-loop structures have been found in telomeres in other organisms, suggesting that it is the conserved feature of telomere structure.

4. The discovery of telomerase

The solution of the end-replication problem by the telomere was confirmed by the discovery of telomerase by Greider and Blackburn (1985). Telomerase was identified in *Tetrahymena* as a specialized enzyme that adds the telomeric G-rich sequence to the end of linear DNA. The addition of telomeric DNA by telomerase explained how the loss of terminal sequences caused by normal semi-conservative replication is counteracted. Telomerase is inactive in adult human cells, and telomere length gradually decreases during cellular senescence (de Lange et al., 1990). By contrast, telomerase is activated after immortalization (Counter et al., 1992).

The telomerase enzyme was co-purified with an RNA moiety, telomerase RNA (TERC), which specifies the sequence of telomeric repeats (Yu et al., 1990). Its catalytic subunit,

identified by genetic screening in yeast (Lendvay et al., 1996) and biochemical purification from the ciliate *Euplotes aediculatus* (Lingner et al., 1996), contains the conserved motif for reverse transcriptase, and it was thus termed telomerase reverse transcriptase (TERT). Forced expression of *TERT* in mortal human cells can bypass senescence (Bodnar et al., 1998), proving that replicative senescence is caused by lack of *TERT* expression.

Other telomerase-associated proteins have been described. They are thought to be involved in the biogenesis of telomerase or to regulate the recruitment of telomerase to chromosome ends. For example, Est1 in budding yeast was identified as a protein whose deficiency reduced telomere length and cell viability after successive rounds of division (Lundblad & Szostak, 1989), and is now known to be involved in the loading of telomerase to telomeric DNA (Taggart et al., 2002).

5. Components of the telomere

5.1 Telomere binding proteins and the protein-counting model for telomere length control

In both mammals and yeast, telomerase-positive cells maintain telomeres at a constant length. Newly formed short telomeres are elongated such that they reach the length that is characteristic of the particular cell type, while over-elongated telomeres shorten until they reach the normal length (Negrini et al., 2007; Marcand et al., 1999). These observations indicate that telomerase activity is regulated at individual ends, and is regulated so as to counteract the loss of telomeric repeats due to the end-replication problem. Recent studies have elucidated the regulatory mechanism that ensures length homeostasis at every telomeric end: the protein complex that binds at double-stranded telomeric DNA exerts an inhibitory effect on telomerase activity.

In budding yeast, the telomere dsDNA-binding protein Rap1 serves to limit telomere length: the number of repeats at an individual telomere was reduced when hybrid proteins containing Rap1 were targeted there by a heterologous DNA-binding domain (Marcand et al., 1997). Through its C-terminal domain, Rap1 interacts with two proteins, Rif1 and Rif2. These two proteins act as telomerase inhibitors, and loss of either protein leads to telomere over-elongation (Hardy et al., 1992; Wotton and Shore, 1997). Thus, a model has been proposed to explain the regulation of telomere length: longer telomeres carrying numerous Rap1 binding sites, leading to the increased binding of telomerase inhibitors, which repress telomerase-dependent telomere elongation. Telomere length declines progressively with each replication cycle, causing the loss of telomere inhibitors at the ends of telomeres, allowing telomere repeat number to be restored by the action of telomerase. Consistent with this model, telomerase is not active at each telomere during every replication cycle, but is activated when the length of the repeat tract is reduced to a threshold level as a result of successive rounds of replication (Teixeira et al., 2004).

In fission yeast, the double-stranded DNA-binding protein Taz1 recruits Rif1 and Rap1 (Kanoh & Ishikawa, 2001; Chikashige & Hiraoka, 2001). Rap1 does not interact directly with Rif1 but, instead, interacts with Poz1, which serves as a negative regulator of telomere length (Miyoshi et al., 2008). In mammals, TRF1 and TRF2 bind to double-stranded telomeric DNA and exert *cis*-inhibitory effects on telomerase activity (Ancelin et al., 2002). They also recruit other proteins to assemble the six-protein shelterin complex (TRF1/TRF2/RAP1/TIN2/TPP1/POT1). All the components of shelterin have been shown to act as negative regulators of telomerase (Smogorzewska & de Lange, 2004)..

5.2 The CST complex

The proteins directly bound to the very ends of chromosomes are not only essential for protecting telomeres but are also involved in recruiting telomerase to chromosomes. A budding yeast *cdc13* mutant, originally isolated as a cell division cycle mutant, displays G₂ arrest after transfer to the restrictive temperature (Hartwell et al., 1973). Cdc13 forms a complex with Stn1 and Ten1 *in vivo* (Grandin et al., 1997; Grandin et al., 2001). Each component of the Cdc13-Stn1-Ten1 heterotrimeric complex (CST complex) has a single-stranded DNA binding motif, the OB-fold domain (Mitton-Fry et al., 2002). As a result, CST has a strong affinity for single stranded telomeric DNA, and thus localizes to the very ends of chromosomes (Taggart et al., 2002). Based on structural and functional similarities, CST has been proposed to be a telomere-specific replication protein A (RPA)-like complex (Gao et al., 2007). Cell cycle arrest in the *cdc13* mutant is due to loss of telomere protection: when CST function is disrupted, capping is dysfunctional and chromosome ends suffer the same fate as DSBs (Garvik et al., 1995). Moreover, the CST complex contributes to telomere replication by directly interacting with the telomerase-associated protein Est1 and DNA polymerase α (Qi and Zakian, 2000; Grossi et al., 2004). Cdc13 is phosphorylated at multiple sites by Cdk and Tel1 kinases (Li et al., 2009; Tseng et al., 2006). These modifications are thought to be important for recruitment of Est1 and telomerase to telomeres.

Although the organization of DNA ends is well conserved, mammalian telomere ends are primarily protected by a Pot1-Tpp1 complex, part of the larger shelterin complex (Wang et al., 2007). Components of shelterin have also been found in fission yeast and plants (Baumann & Cech, 2001; Miyoshi et al., 2008; Shakirov et al., 2005). Budding yeast CST and shelterin components do not have sequence similarity, suggesting that budding yeast may have a unique mode of telomere capping. However, recent studies have revealed that mammals and plants have Stn1 and Ten1 homologs, and that the two proteins form a complex with another protein called Ctc1 (Miyake et al., 2009; Surovtseva et al., 2009). The Ctc1-Stn1-Ten1 heterotrimeric complex associates with single-stranded DNA but with no sequence specificity. Human Ctc1 and Stn1 have been characterized as proteins that stimulate DNA polymerase α activity (Casteel et al., 2009) and appear to play a role in replication of "difficult" sites, including telomeric repeats.

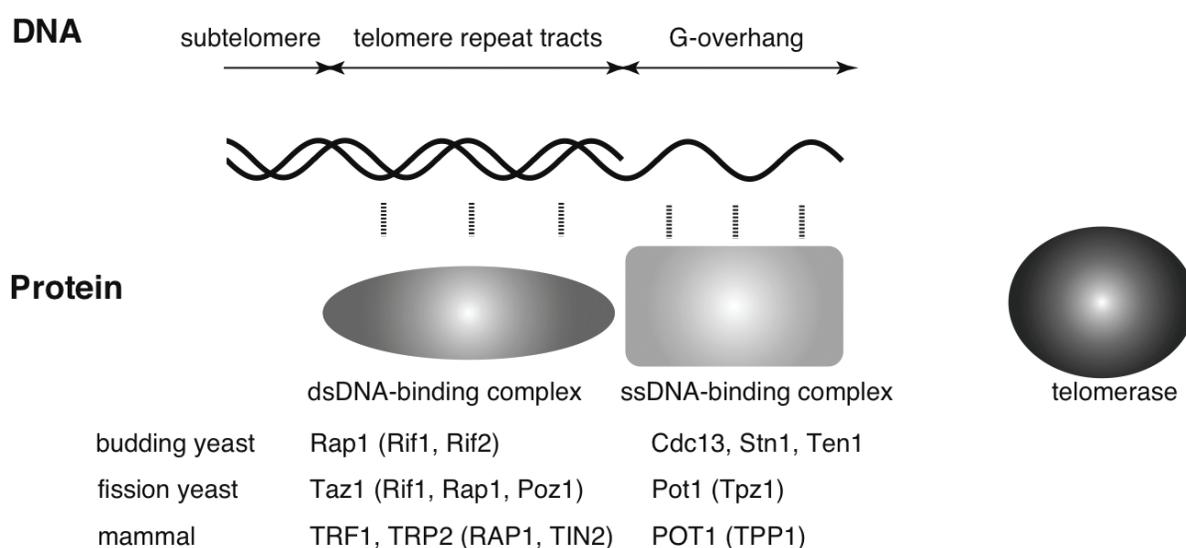


Fig. 1. Telomere DNA structure and the binding proteins in model organisms

5.3 Proteins involved in telomere replication

5.3.1 DNA repair proteins

One critical function of the telomere is assumed to be the prevention of normal chromosome ends being recognized as a damaged DNA ends. This is mediated by the formation of a specialized nucleoprotein complex. Paradoxically, however, telomere length is reduced by mutations in DSB-detection machineries such as Tel1 and the MRX (Mre11-Rad50-Xrs2) complex, indicating that proteins involved in the recognition and repair of DNA damage are important for telomere homeostasis (Greenwell et al., 1995; Nugent et al., 1998). Epistasis analysis has established that MRX and Tel1 act in the telomerase pathway of telomere maintenance (Ritchie & Petes, 2000), and that Mre11 and Tel1 are required for the recruitment of telomerase to telomeres (Goudsouzian et al., 2006). Therefore, these proteins are involved in telomere length control as components of the telomerase-dependent telomere elongation pathway.

5.3.2 DNA polymerases

A DNA polymerase α /primase complex is responsible for initiating *de novo* lagging strand DNA synthesis. In budding yeast, mutations in Pol α lead to telomerase-dependent telomere elongation and a telomerase-independent increase in G-overhang length during the S phase (Adams et al., 1996; Adams Martin et al., 2000). Moreover, Pol α is essential for telomerase-dependent addition of telomeric DNA to DSBs (Diede & Gottschling, 1999).

The Pol α complex physically interacts with the CST complex in budding yeast, while an analogous association between the lagging strand replication machinery and telomerase has been observed in ciliate and fission yeast. Pol α is also implicated in telomere replication in higher eukaryotes: G-overhang length is increased in a mouse cell line with a temperature-sensitive Pol α allele (Nakamura et al., 2005). As a mutation in replication protein C was also shown to lead to telomere elongation (Adams et al., 1996), it has been suggested that switching from polymerase α to replication factor C during lagging strand synthesis is critical for the regulation of telomerase activity.

5.3.3 Replication protein A

Replication protein A (RPA) is a heterotrimeric complex that binds to and stabilizes single-stranded DNA intermediates produced during various DNA metabolic processes, including DNA replication. RPA localizes to telomeres during the S phase (Schramke et al., 2004; Takata et al., 2005). Yeast cells harboring an RPA mutation were shown to have shortened telomeres (Ono et al., 2003).

5.3.4 DNA helicase

Telomeric DNA has the specialized structure described above, which may affect the progression of replication forks at the locus. Indeed, replication forks stall or pause at telomeres in yeast and human cells (Ivessa et al., 2002; Sfeir et al., 2009). Such difficulties seem to be overcome, at least partially, by some of the telomere-binding proteins. For example, in fission yeast, Taz1 contributes to the efficient replication of telomeres by preventing fork stalling (Miller et al., 2006). RecQ-type DNA helicases have been shown to facilitate telomere replication, probably by relieving the secondary DNA structure at telomeres (Sfeir et al., 2009).

6. Mechanism of telomerase recruitment during the cell cycle

Consistent with the requirement for a free 3' single-stranded DNA end as a substrate for *in vitro* telomerase assay, a 3' overhang in the G-rich strand at the end of chromosomes is critical for telomerase action. In budding yeast, the single-strand overhangs are present throughout the cell cycle, but are relatively short (10-15 nucleotides) for most of the cycle. The length of the overhangs increases transiently in the late S phase, during which telomere replication takes place (Marcand et al., 2000; Larrivee et al., 2004). The cell cycle-dependent formation of G-overhangs is mediated by the cyclin-dependent kinase Cdk1 (Cdc28-Clb in budding yeast), which is activated in the S and G₂/M phases (Frank et al., 2006; Vodenicharov & Wellinger, 2006).

Telomerase activity is indispensable for G-overhang formation during the S phase in yeast and mammals. Nucleolytic end processing activity also contributes to G-overhang formation (Wellinger et al., 1996). MRX in budding yeast and its mammalian ortholog, MRN (Mre11-Rad50-Nbs1), are important for G-overhang formation (Diede and Gottschling, 2001; Takata et al., 2005; Chai et al., 2006). Their activity is regulated by the associated protein Sae2, a target of Cdk1 (Huertas et al., 2008). However, at least in yeast, a redundant nucleolytic activity regulated by Sgs1 (RecQ) also controls end processing at telomeres (Bonetti et al., 2009). Interestingly, the MRX complex only binds to leading-strand telomeres, and this binding is critical for the binding of the CST complex and telomerase to leading-strand telomeres (Faure et al., 2010). As described above, genetic analysis has shown that MRX and telomerase act in the same pathway. This suggests that telomere elongation probably occurs mainly at leading-strand telomeres, at least in yeast. The leading strand polymerase Pole arrives at telomeres earlier than the lagging strand DNA polymerases Pol α and Pol δ (Moser et al., 2009). Thus, temporal regulation may contribute to the difference between the two strands. In mammalian cells, differences in the behaviors of leading- and lagging-strand telomeres have been also reported, such as the preferential occurrence of telomere-telomere fusions between leading-strand telomeres upon shelterin inactivation (Bailey et al., 2001).

7. Summary of telomeric DNA replication: an overview based on studies of budding yeast

Figure 2 presents a current model for telomere replication. In this model, telomere integrity is thought to be maintained by an elegant mechanism. The switch from a protected state to an accessible state allows telomerase recruitment. As discussed previously, this is achieved in both a cell cycle-dependent manner and a telomere length-regulated manner.

1. Replication fork progression. In yeast, telomeres replicate during the late S phase (Raghuraman et al., 2001). Replication is initiated from a replication origin located in the subtelomeric region, and the replication fork moves towards the chromosome terminus. In mammalian cells, the timing of telomere replication seems not to be restricted to the late S phase (Wright et al., 1999), and the direction of fork movement at telomeres is ambiguous.
2. End processing. After the replication fork reaches the terminus, C-strand-specific resection takes place to produce the G-overhang.
3. Recruitment of telomere proteins. Single-stranded DNA-binding complexes are recruited to the extended G-overhang. RPA may compete with CST or Pot1 for binding sites, but ultimately RPA is displaced by telomere-specific components. In mammalian

- cells, telomeric repeat-containing RNA (TERRA) facilitates the RPA-to-Pot1 switch (Flynn et al., 2011).
4. Recruitment of telomerase. Usually, recruitment of Tel1 to telomeres is inhibited by Rif1 and Rif2 (Hirano et al., 2009). The conformation of short telomeres with reduced amounts of these two proteins changes to the accessible state, and Tel1 is thus recruited. Tel1 phosphorylates Cdc13 (and probably other proteins), thereby enabling it to interact with Est1 and permitting the telomerase to load to the ends of telomeres. It is not clear at present whether this regulatory mechanism is conserved among Tel1 orthologs in mammals and fission yeast.
 5. Telomere elongation and C-strand filling. G-overhangs are elongated by the action of telomerase. Then, CST recruits the Pol α complex to coordinate the synthesis of the complementary C-strand. The replicated telomere now returns to the protected state.

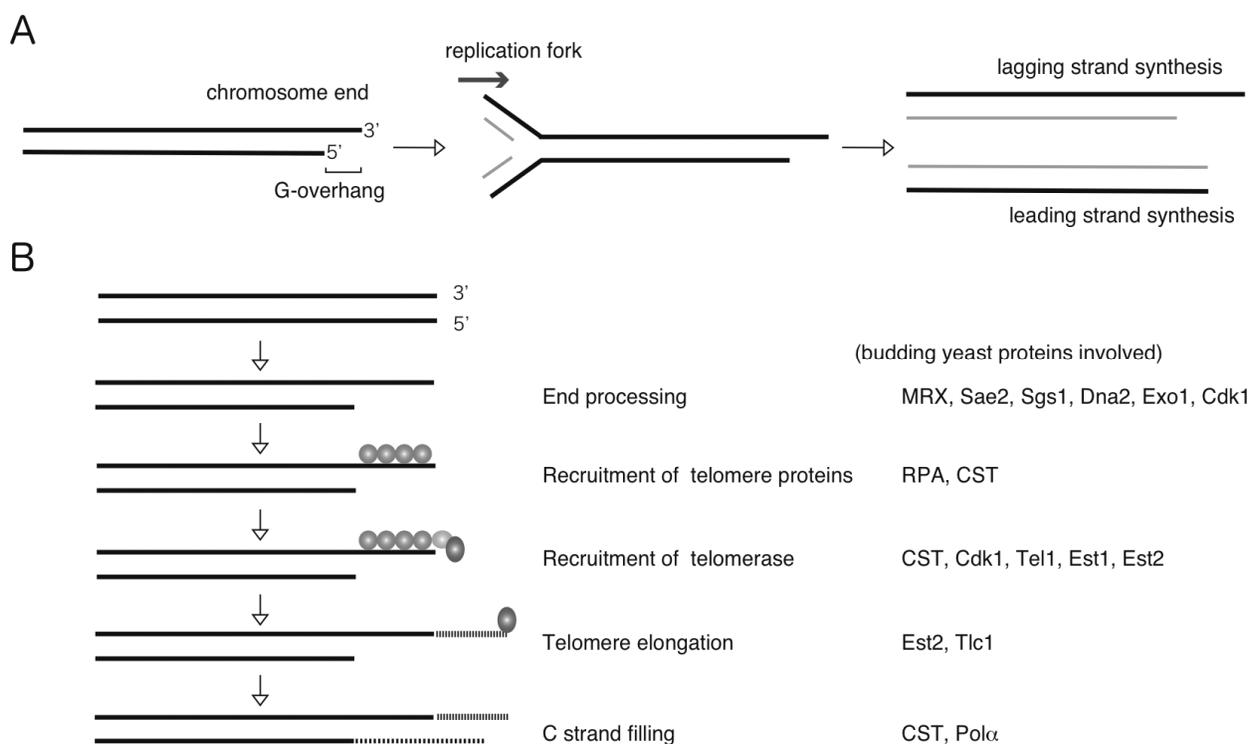


Fig. 2. Model for telomere replication in budding yeast. A: Fork movement towards the chromosome terminus. B: Telomerase-dependent telomere elongation.

8. Alternative mechanisms that bypasses telomerase deficiency

In budding yeast, telomerase-defective mutants gradually lose their proliferation capacity because of telomere shortening. However, a fraction of cells recovered viability without telomerase activity after prolonged periods of culturing. These “survivor” cells were found to acquire the potential to elongate chromosome ends through a recombination-mediated process (Lundblad & Blackburn, 1993). They are categorized as either type I or type II cells on the basis of their telomere composition and mode of maintenance (Teng & Zakian, 1999). Type I cells have a very short telomere repeat tract, but have amplified subtelomeric Y' sequences. By contrast, type II cells have long heterogeneous telomere repeats. Telomere maintenance in both cell types requires the homologous recombination gene *RAD52* (Le et

al., 1999). The change in the survivor cells is likely to be epigenetic, and both types of telomerase-independent telomere maintenance are inherited as a non-Mendelian trait that is dominant over senescence (Makovets et al., 2008), although the exact mechanism remains unknown.

Similar mechanisms for escaping telomere dysfunction have also been observed in fission yeast. The genome of this organism consists of three chromosomes, and a population of cells can overcome the loss of telomerase by the recombination-mediated process (Nakamura et al., 1998). In addition, some survivor cells possess three circular chromosomes produced by end-to-end fusion between the arms of a chromosome. Cells harboring circular chromosomes can propagate normally by mitosis, but are unable to produce viable spores through meiosis (Naito et al., 1998; Nakamura et al., 1998). The requirement of chromosome linearity for normal chromosome segregation during meiosis has been discussed (Ishikawa & Naito, 1999).

Some cancer cell lines grow in spite of a lack of telomerase activity. Such cell lines show high heterogeneity in telomere length (Murnane et al., 1994) and are thought to elongate telomere sequences via a telomerase-independent, alternative lengthening of telomere (ALT) mechanism. Involvement of recombination in ALT was subsequently confirmed (Dunham et al., 2000), although its exact mechanism is still being debated.

9. Regulation of telomeres and telomerase during development and reprogramming

Telomerase activity is tightly regulated during vertebrate development, being high in male germ cells, low in mature oocytes and cleavage stage embryos, and high in blastocysts (Hiyama & Hiyama, 2007). In spite of the low telomerase activity during early cleavage development, telomeres in zygotes are remarkably long at the first cell division. Interestingly, telomere lengthening at this stage was observed in parthenote embryos derived from telomerase-null mice, indicating that it depends on factors of maternal origin and does not require telomerase (Liu et al., 2007). The recombination protein Rad50 is localized at telomeres during the early cleavage cycle, suggesting that telomere lengthening following fertilization is recombination-dependent. Recently, *Zscan4*, a protein that is expressed specifically in the two-cell stage embryo, was shown to be involved in this process (Zalzman et al., 2010). Activity of this alternative telomere maintenance mechanism decreases before the blastocyst stage, during which the telomerase-dependent mechanism is reestablished. Expression of telomerase is maintained in the stem cell compartment of several adult tissues, although telomerase levels in these tissues are not sufficient to prevent progressive telomere shortening with age in either humans or mice (Flores et al., 2008).

Embryonic stem (ES) cells and undifferentiated embryonal carcinoma (EC) cells display high levels of telomerase activity and *TERT* expression, both of which are rapidly downregulated during differentiation (Armstrong et al., 2005). Telomere length is elongated during the establishment of induced pluripotent stem (iPS) cells (Marion et al., 2009), which is associated with induction of the *TERT* gene. These observations suggest that acquisition of the capacity for indefinite self-renewal may be linked to the regulation of telomerase activity. Interestingly, in spite of their high telomerase activity, ES cells also express *Zscan4*. Knockdown of *Zscan4* in ES cells shortens telomeres, increases karyotype abnormalities, and consequently reduces cell proliferation (Zalzman et al., 2010). Thus, a unique mode of telomere maintenance may operate in ES cells.

10. Consequences of telomere shortening

During replicative senescence in human somatic cells, dysfunction caused by telomere shortening is sensed by DNA damage signals that induce cell cycle arrest via the p53 pathway (d'Adda di Fagagna et al., 2003). In cells in which p53 is mutated, dysfunctional telomeres promote genome instability and progression to cancer, indicating that replicative senescence contributes to the suppression of tumorigenesis (Chin et al., 1999). Moreover, increasing evidence implicates telomere dysfunction in age-related pathogenesis, such as progressive atrophy and functional decline in high-turnover tissues (Sahin and Depinho, 2010).

Although the hallmark of senescent cells is irreversible growth arrest, several responses besides those related to the cell cycle have been observed. Senescent cells develop an enlarged morphology, upregulate senescence-associated β -galactosidase (SA- β gal) activity, and show changes in metabolism, chromatin organization, and gene expression (Dimri et al., 1995; Funayama et al., 2006; Sahin et al., 2011). Moreover, senescent cells display a senescence-associated secretory phenotype (SASP), which is associated with increased secretion of cytokines and matrix metalloproteinases (Coppe et al., 2008). The mechanisms underlying the induction of these diverse phenotypes are largely unknown, although p38MAPK has been suggested to be involved (Freund et al., 2011).

Using telomerase-defective budding yeast cells as a model, mechanisms underlying the cellular responses to telomere shortening have been extensively studied. Genome-wide analysis of changes in gene expression showed that telomere-shortened cells have a unique transcriptional profile that shares features of DNA damage responses and environmental stress responses, and that is characterized by up-regulation of energy production genes (Nautiyal et al., 2002). Telomere shortening induces an increase in cell size, which is mediated by the DNA damage checkpoint kinase Mec1. Cell size expansion is associated with the enlargement of a vacuole that serves as a prominent lytic compartment in yeast. As a deficiency in vacuolar morphogenesis reduces the viability of telomere-shortened cells (Matsui & Matsuura, 2010), vacuolar function(s) may contribute to senescence-associated physiology.

11. The pathology of telomerase disorders

Several human disorders have been directly linked to reduced telomerase activity. Dyskeratosis congenita (DC) is an inherited disorder characterized by the degeneration of multiple tissues, including bone marrow. The mutations that cause DC have been implicated in telomere metabolism. X-chromosome-linked DC is caused by mutations in the *DKC1* gene, which encodes dyskerin, an RNA-binding protein that stabilizes TERC (Mitchell et al., 1999). Causative mutations for other DC subtypes of DC have been mapped to *TERT* and *TERC* itself. Cells from DC patients have shorter telomeres and display premature senescence (Westin et al., 2007). The pathology of DC demonstrates the critical importance of telomerase in humans, especially in the maintenance of stem cells (Kirwan & Dokal, 2009).

The Werner syndrome (WS) is a premature aging syndrome. Fibroblasts from WS patients show accelerated telomere attrition, while the gene responsible for WS, *WRN*, encodes a DNA helicase involved in DNA replication, especially at telomeres (Crabbe et al., 2004). Ataxia telangiectasia (AT) is another premature aging syndrome that is characterized by

marked telomere attrition. The gene responsible for AT, *ATM*, is the ortholog of the budding yeast gene *TEL1* and plays key roles in DNA damage signaling (Varizi, 1997).

The causal link between telomere shortening and the aging phenotype at the organism level was demonstrated in a series of genetic studies performed using mouse models. Experimental mice usually have extremely long telomeres, and *Wrn*- and *Atm*-knockout mice do not display a premature aging phenotype. However, if they are subjected to telomere-limiting conditions by crossing with telomerase-null mice, they exhibit an accelerated aging phenotype (Chang et al., 2004; Wong et al., 2003). This observation suggests that telomere shortening is rate-limiting for the pathogenesis of premature aging syndromes.

12. Extra-telomeric roles of telomerase

Mice with modifications in genes encoding telomerase components have demonstrated the role of telomere length in maintaining stem cells (Jaskelioff et al., 2011). In contrast, *Tert* overexpression has an anti-aging effect in mice. This effect is not seen in *Terc*-deficient mice (Tomas-Loba et al., 2008), indicating that telomerase activation is the main mechanism underlying it.

There is evidence that telomerase has extra-telomeric functions in stem cell maintenance, acting as a transcriptional modulator of the Wnt- β -catenin pathway (Park et al., 2009). It also exhibits RNA-dependent RNA polymerase activity as a complex with the RNA component of mitochondrial RNA processing ribonuclease (RMRP) (Maida et al., 2009). It is still not known whether these extra-telomeric functions are conserved in telomerase enzymes from other species.

13. Conclusion

Extensive studies using unicellular organisms have revealed that a wide variety of proteins are involved in telomere homeostasis, and it becomes evident that coordination between their actions contributes to the regulation of telomere replication. The emerging evidence now suggests that the regulatory mechanism is linked directly with development and pathogenesis of mammals. Further dissection of the regulatory network may shed light on novel strategies for the management of telomere-related physiologies such as aging and cancer.

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The study of DNA advanced human knowledge in a way comparable to the major theories in physics, surpassed only by discoveries such as fire or the number zero. However, it also created conceptual shortcuts, beliefs and misunderstandings that obscure the natural phenomena, hindering its better understanding. The deep conviction that no human knowledge is perfect, but only perfectible, should function as a fair safeguard against scientific dogmatism and enable open discussion. With this aim, this book will offer to its readers 30 chapters on current trends in the field of DNA replication. As several contributions in this book show, the study of DNA will continue for a while to be a leading front of scientific activities.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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