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Roles of DNA Repair Proteins in Telomere Maintenance

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1. Introduction

Most eukaryots have specialized protein-DNA complexs, called telomeres at the ends of natural linear chromosomes. Telomeric DNA consists of a tandemly repeated G-rich sequence. The lengths of telomeric DNAs in *S. pombe*, *S. cerevisiae,* and human are ~300 nucleotids, ~350 nucleotides, and ~10 kb, respectively. The ends of the telomeric DNA have 3′ single-stranded overhangs. The protein components of telomeres consists of double-stranded telomere-binding proteins, such as human TRF1 and TRF2, S. pombe Taz1, and single-stranded telomere-binding proteins, such as *S. cerevisiae* Cdc13, *S. pombe* Pot1, and human POT1. DNA double-strand breaks (DSBs) must be repaired to maintain genomic integrity. In contrast, natural chromosome ends should not be recognized as DSBs. The telomere is capped to protect from DNA repair activity. If this capping function is lost, this uncapped telomere is recognized as DNA damage and becomes substrate for DNA repair proteins. The first step in homologous recombination (HR) repair is processing of DNA ends by 5′ to 3′ degradation to create 3′ single-stranded overhangs. The proteins involved in this steps include *S. cerevisiae* Mre11-Rad50-Xrs2 complex (MRX), Sae2, Sgs1, and Dna2. Recent works revealed that proteins involved in the processing of DNA DSB ends are also involved in the processing of capped or uncapped telomere. These facts raised new question of how these proteins are regulated at telomere ends. This chapter will focus on the roles of proteins involved in the processing of DBS ends at capped (functional) and uncapped (dysfunctional) telomere in *S. pombe*, *S. cerevisiae* and human. This chapter will also focus on the functional interactions between telomere-binding proteins and proteins involved in the processing of DBS ends. Resent works revealed that double-stranded and single-stranded telomere-binding proteins play critical roles to control proteins involved in DNA repair at chromosome ends.

2. Roles of proteins involved in DNA end-processing in telomere maintenance

DNA DSBs are repaired by HR or non-homologous end-joining (NHEJ) [1]. *S. cerevisiae* MRX is involved in both HR and NHEJ [2]. MRX is suggested to be involved in the processng of DSB ends in HR repair. Recently, several other proteins involved the processing have been discovered. Some of the these proteins are also involved in the processing of telomere ends. In this section, the roles of these proteins in telomere maintenance will be discussed.

2.1 Roles of proteins involved in DNA end-processing at DSB ends

Role of *S. cerevisiae* MRX in HR is well studied both in vivo and in vitro (Mimitou and Symington 2009) (Mimitou and Symington 2008) (Zhu et al. 2008) (Gravel et al. 2008) (Cejka et al. 2010) (Niu et al. 2010). MRX cooperates with Sae2 to initiate 5′ resection at DNA DSB end. Although both MRX and Sae2 have nuclease activities, it remains unclear the contribution of these nucleases to DSB resection. The resultant 3′ single-stranded ovehangs are further resected by two redundant pathways. One is dependent on Sgs1 helicase, a conserved RecQ family member, and the Dna2. Dna2 has both helicase and nuclease domains, but nuclease activity is enough for DSB resection (Zhu et al. 2008). The other is dependent on Exo1 5′-3′ exonuclease. *S. cerevisiae* Yku70-Yku80 heterodimer (Ku) binds to DSB ends and recruits downstream NHEJ factors (Critchlow and Jackson 1998). Ku inhibits 5′ resection by MRX (Mimitou and Symington 2010) (Shim et al. 2010). Similar model is proposed in *S. pombe*(Tomita et al. 2003). *S. pombe* Mre11-Rad50-Nbs1 (S. cerevisiae Xrs2 homologue) complex (MRN) is also suggested to be involved in 5′ resection at DNA DSB end. *S. pombe* Ku also inhibits 5′ resection by MRN. In the absence of MRN, Exo1 can resect DSB ends. Contribution of *S. pombe* RecQ helicase Rqh1 and Dna2 in the resection of DSB ends remains unclear. It has been shown that human BLM, a RecQ helicase family, and DNA2 interact to resect DNA end and helicase activity of BLM and nuclease activity of DNA2 are required for this reaction (Nimonkar et al. 2011). The functional conservation of these proteins from yeast to human suggests that the functions of these proteins in *S. pombe* are also conserved.

2.2 Roles of proteins involved in DNA end-processing in telomere maintenance in *S. pombe* and in *S. cerevisiae*

Telomere ends should not be recognized as DSB ends, because telomere ends should no be repaired by HR or NHEJ. However, proteins involved in HR or NHEJ are also involved in telomere maintenance (Longhese et al. 2010). The chromosome end replicated by lagging-strand synthesis has 3′ single-stranded overhangs. In contrast, the chromosome end replicated by leading-strand synthesis is blunt-end. However, most eukaryotes have 3′ single-stranded overhangs at both ends, suggesting that the chromosome end replicated by leading-strand synthesis is resected (Wellinger et al. 1996; Makarov, Hirose, and Langmore 1997). *S. cerevisiae* MRX is suggested to be involved in this resection (Diede and Gottschling 2001). However, MRX independent resection has been suggested, which may be produced at lagging-strand telomere after DNA replication without any nuclease activity (Larrivee, LeBel, and Wellinger 2004). MRX mainly binds to the leading-strand telomere, further suggesting that MRX is involved in this resection at leading-strand telomere (Faure et al. 2010). An inducible short telomere assay revealed that artificial telomere ends is resected by the same DNA repair factors (Bonetti et al. 2009) (Longhese et al. 2010) (Iglesias and Lingner 2009) (Fig. 1). MRX and Sae2 act in the same resection pathway. Concomitant inactivation of Sae2 and Sgs1 abolishes end resection, suggesting that they have redundant function for the resection. Dna2 acts redundantly with Exo1, but not with Sgs1, suggesting that Dna2 supports Sgs1 activity. The lack of Sgs1, Dna2 or Exo1 by itself does not affect the resection, suggesting that Exo1 and Sgs1-Dna2 may less important for the resection than MRX and Sae2. These results were obtained by using artificial telomere, which initially produces blunt-end telomere by nuclease. However, leading-strand synthesis in wild-type cells also produces blunt-end telomere. Consistently, Sae2 and Sgs1 also play redundant functions in natural telomere end-processing (Bonetti et al. 2009), suggesting that an inducible short

telomere assay mimic wild-type telomere end. In wild-type *S. cerevisiae* cells, 3′ single-stranded overhangs increase in S phase at telomeres (Wellinger, Wolf, and Zakian 1993) (Dionne and Wellinger 1996). In contrast, 3′ single-stranded overhangs can be detected at telomeres throughout the cell cycle in the absence of *S. cerevisiae* Ku, suggesting that Ku inhibits resection at telomere (Gravel et al. 1998) (Polotnianka, Li, and Lustig 1998). This function of Ku is conserved in *S. pombe* Ku (Kibe et al. 2003). However, proteins involved in the resection of telomere ends are not well studied in *S. pombe*. In *S. pombe*, Dna2 is involved in the resection of telomere ends (Tomita et al. 2004).

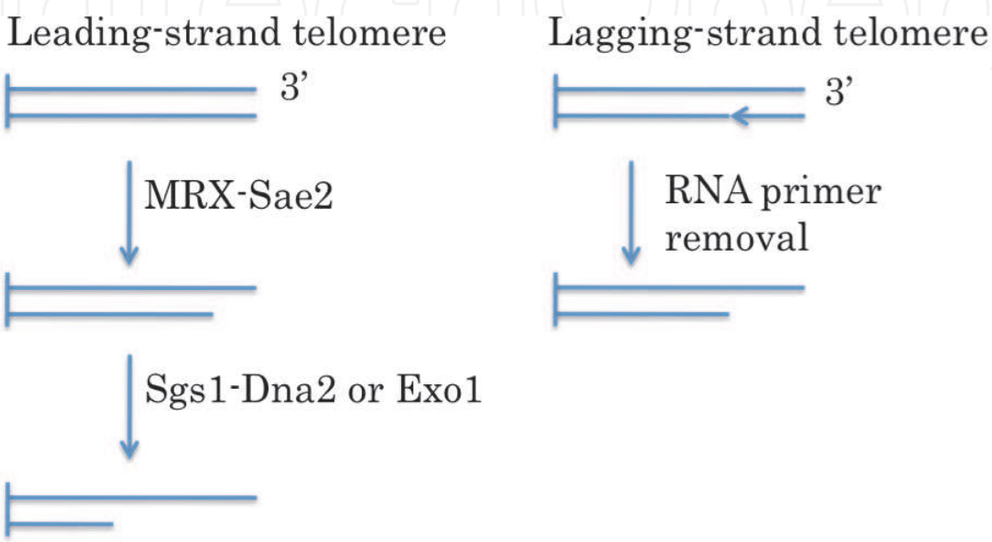

Fig. 1. Model for DNA end-processing at *S. cerevisiae* telomere. DNA replication will create blunt-end at leading-strand telomere and 3′ single-stranded overhangs at lagging-strand telomere after removal of the last RNA primer. Similar to the case at DSB ends, MRX and Sae2 play a major role to produce 3′ single-stranded overhangs at telomeres. Sgs1-Dna2 and Exo1 can provide compensatory activities to produce 3′ single-stranded overhangs.

2.3 Proteins involved in DNA end-processing in *S. pombe taz1Δ* cells

S. pombe Taz1 binds telomeric double-stranded DNA (Cooper, Watanabe, and Nurse 1998). Deletion of *taz1* causes massive telomere elongation. Asynchronous wild-type *S. pombe* cells have small amount of 3′ single-stranded overhangs (Kibe et al. 2003). In contrast, *taz1* disruptant has very long 3′ single-stranded overhangs (Tomita et al. 2003). In this mutant background, roles of MRN, Ku, Dna2, and Exo1 are studied (Fig. 2). MRN and Dna2 are responsible for the production of 3′ single-stranded overhangs (Tomita et al. 2004). But, 3′ single-stranded overhangs are produced by concomitant deletion of Ku and MRN, suggesting that unknown nuclease can produce the overhangs in the absence of both MRN and Ku in *taz1* disruptant. Exo1 is not involved in this activity. Telomere ends in *taz1* disruptant is partially unprotected. Indeed, RPA foci and Rad22^{Rad52} foci are produced at telomere in *taz1* disruptant (Carneiro et al. 2010). Therefore, proteins involved in the resection in *taz1* disruptant may not be same as that in wild-type cells. However, Dna2 is involved in the resection in both wild-type and *taz1Δ* background, suggesting that some of the proteins involved in the resection in *taz1* disruptant are also involved in the resection in wild-type cells.

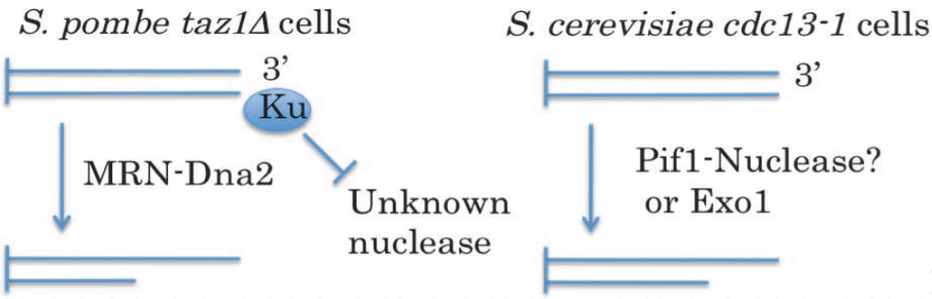

Fig. 2. Model for DNA end-processing at dysfunctional telomere. 3' single-stranded overhangs are produced by MRN and Dna2 in *S. pombe taz1Δ* cells (Left). Ku inhibits unknown nuclease, but not nuclease activity depending on MRN-Dna2. 3' single-stranded overhangs are produced by Pif1 or Exo1 in *S. cerevisiae cdc13-1* cells (Right). Unknown nuclease is suggested to function together with Pif1 helicase.

2.4 Proteins involved in DNA end-processing in *S. cerevisiae cdc13-1* cells

S. cerevisiae Cdc13 binds telomeric single-stranded DNA (Garvik, Carson, and Hartwell 1995). *cdc13-1* temperature sensitive mutant is used to study proteins that are involved in the resection at uncapped telomeres (Lydall 2009). These studies revealed that the single-stranded DNA at telomeres in *cdc13-1* mutants resembles a DSB end. However, there are some differences between these ends (Fig. 2). In *cdc13-1* mutants at high temperature, Pif1 helicase and Exo1 are redundantly involved in the resection of uncapped telomere (Dewar and Lydall 2010). It remains unclear how Pif1 contribute to the resection. As Pif1 has no nuclease activity, involvement of the unknown nuclease is suggested to cleave single-stranded DNA unwound by Pif1 helicase. Sgs1 also contributes to resection of telomeres in *cdc13-1* mutants (Ngo and Lydall 2010). However, unlike *pif1 exo1* double mutant, resection of telomeres in *cdc13-1* mutant background occurs in *sgs1 exo1* double mutant, demonstrating that Pif1 and Exo1 play major roles in the resection of uncapped telomere at high temperature.

3. Roles of RecQ helicase in telomere maintenance

RecQ helicase is conserved from *E. coli.* to human and play a critical role in genome stability (Bernstein, Gangloff, and Rothstein 2010). Werner Syndrome (WS) is a premature aging syndrome resulting from loss of function of one of the human RecQ helicase WRN. The roles of *S. cerevisiae* RecQ helicase Sgs1 in homologous recombination are well studied. RecQ helicase is also involved in telomere maintenance especially at dysfunctional telomere. In this section, roles of RecQ helicase in telomere maintenance will be discussed. Functional interaction between RecQ helicase and POT1 in *S. pombe* and in human will be also discussed.

3.1 Roles of RecQ helicase in DNA repair

S. cerevisiae RecQ helicase Sgs1 is involved in several steps in HR (Ashton and Hickson 2010). As discussed above, Sgs1 is involved in the resection of DSB ends. Genetic and in vitro studies also suggest that Sgs1 inhibits unscheduled recombinogenic events, but promotes the resolution of recombination intermediates. Strains deleted for *SGS1* display hyperrecombination phenotype, but are defective in DNA damage-induced heteroallilic

recombination (Watt et al. 1996) (Onoda et al. 2001). *S. cerevisiae* Sgs1 and Top3 migrate and disentangle a double Holliday junction (dHJ) to produce non-crossover recombination products in vitro (Cejka et al. 2010). This activity is also detected in human RecQ helicase BLM and human topoisomerase IIIa (Wu and Hickson 2003). Mutant of *S. pombe* RecQ helicase *rqh1* is sensitive to DNA damage and has high frequency of recombination under normal growth conditions and following DNA damage, suggesting that Rqh1 is also involved in HR repair both positively and negatively (Murray et al. 1997) (Stewart et al. 1997) (Doe et al. 2000) (Caspari, Murray, and Carr 2002).

3.2 Roles of RecQ helicase in telomere maintenance in *S. cerevisiae*

As mutation of *S. cerevisiae SGS1* does not affect telomere length, Sgs1 has no apparent role in telomere maintenance in the presence of telomerase activity (Watt et al. 1996). However, the double mutant between telomerase RNA component *TLC1* and *SGS1* shorten telomeres at an increased rate per population doubling and Sgs1 affects telomere-telomere recombination in the absence of telomerase, demonstrating that Sgs1 plays roles at telomere in the absence of telomerase activity (Johnson et al. 2001) (Cohen and Sinclair 2001) (Huang et al. 2001). X-shaped structures are accumulated at telomeres in senescing *tlc1 sgs1* double mutants and these structures are suggested to be the recombination intermediates related to hemicatenanes. This result suggests that Sgs1 is required for the efficient resolution of telomere recombination intermediates in the absence of telomerase (Lee et al. 2007; Chavez, Tsou, and Johnson 2009).

3.3 Roles of RecQ helicase in telomere maintenance in mammals

Human RecQ helicase WRN binds to telomere in S phase in primary human IMR90 fibroblasts and is required for efficient replication of the G-rich telomeric DNA strand, suggesting that WRN is required for replication of telomeric DNA in telomerase-negative primary human fibroblasts (Crabbe et al. 2004). In Werner syndrome (WS) cells, replication-associated telomere loss results in the chromosome fusions, causing genomic instability (Crabbe et al. 2007). The life span of normal human skin fibroblasts derived from WS patients can be extended by expression of the catalytic subunit human telomerase reverse transcriptase (hTERT) (Wyllie et al. 2000; Ouellette et al. 2000). These facts demonstrate that dysfunctional telomere is a major determinant of the premature aging syndrome and WRN plays important role at dysfunctional telomere and telomerase activity can suppress the defect in WRN deficient cells. Consistently, Wrn-deficient mouse, which has telomerase activity, has no disease phenotype, but telomerase-Wrn double null mouse elicits a Werner-like premature aging syndrome (Chang et al. 2004). Telomere sister chromatid exchange (T-SEC) increases in cells from telomerase-Wrn double null mouse, suggesting that WRN are required to repress inappropriate telomere recombination (Laud et al. 2005) (Multani and Chang 2007). Human WRN and other RecQ helicase BLM co-localizes with telomere in human cancer cells that lack telomerase, ALT cells (Johnson et al. 2001; Opresko et al. 2004; Lillard-Wetherell et al. 2004). As telomeres in ALT cells are maintained by HR, human WRN and BLM are suggested to be involved in the recombination at telomere in ALT cells. Possible roles of WRN in telomere maintenance will be discussed in the next section.

3.4 Functional interaction between RecQ helicase and POT1 in *S. pombe* and in human

Pot1 is conserved from *S. pombe* to human and binds to single-stranded telomeric DNA sequence specifically (Baumann and Cech 2001). Deletion of *S. pombe pot1* causes rapid

telomere loss and chromosome circularization and this circularization is mediated by single strand annealing (SSA) (Wang and Baumann 2008). In *S. cerevisiae*, Rad52, Rad1/Rad10 nuclease, RPA, Srs2 helicase, and Sgs1 are involved in SSA (Fishman-Lobell and Haber 1992) (Ivanov and Haber 1995) (Ivanov et al. 1996) (Paques and Haber 1997), (Sugawara, Ira, and Haber 2000; Umezu et al. 1998) (Zhu et al. 2008). Consistently, the double mutants between *S. pombe* homologue of these proteins and *pot1* are synthetically lethal (Wang and Baumann 2008). *S. pombe* telomerase disruptant can survive either by maintaining telomere by HR or chromosome circularization(Nakamura, Cooper, and Cech 1998). In contrast, *pot1* disruptant survives only by chromosome circularization (Baumann and Cech 2001). One possible explanation is that Pot1 is required for prevention of rapid telomere loss, which would lead chromosome circularization dominantly. Recently our group has reported that the double mutant between *rqh1-hd* (helicase dead point mutant) and *pot1* is not synthetically lethal (Takahashi et al. 2011). The chromosome ends of the *pot1 rqh1-hd* double mutant are maintained by HR. There are several possible explanations for this. First, helicase dead Rqh1 may bind to the chromosome ends in *pot1* disruptant to inhibit rapid telomere loss, allowing cells to maintain chromosome ends by HR. Second, helicase activity of the Rqh1 may be involved in the rapid telomere loss in the *pot1* disruptant, because *S. cerevisiae* RecQ helicase is involved in the processing of telomere ends. This will also allow cells to maintain chromosome ends by HR. Third, helicase activity of the Rqh1 may be required for the suppression of recombination at telomere. This will also allow cells to maintain chromosome ends by HR. The exact role of the helicase dead Rqh1 in pot1 disruptant remains unclear. Interestingly, *pot1 rqh1-hd* double mutant is sensitive to anti-microtubule drug thiabendazole (TBZ) (Takahashi et al. 2011). The *pot1 rqh1-hd* double mutant has recombination intermediates even in the M phase at the chromosome ends. This physical link between the sister chromatids in M phase will inhibit chromosome segregation, especially in the presence of TBZ, which would lender cells sensitive to TBZ. Interestingly, concomitant

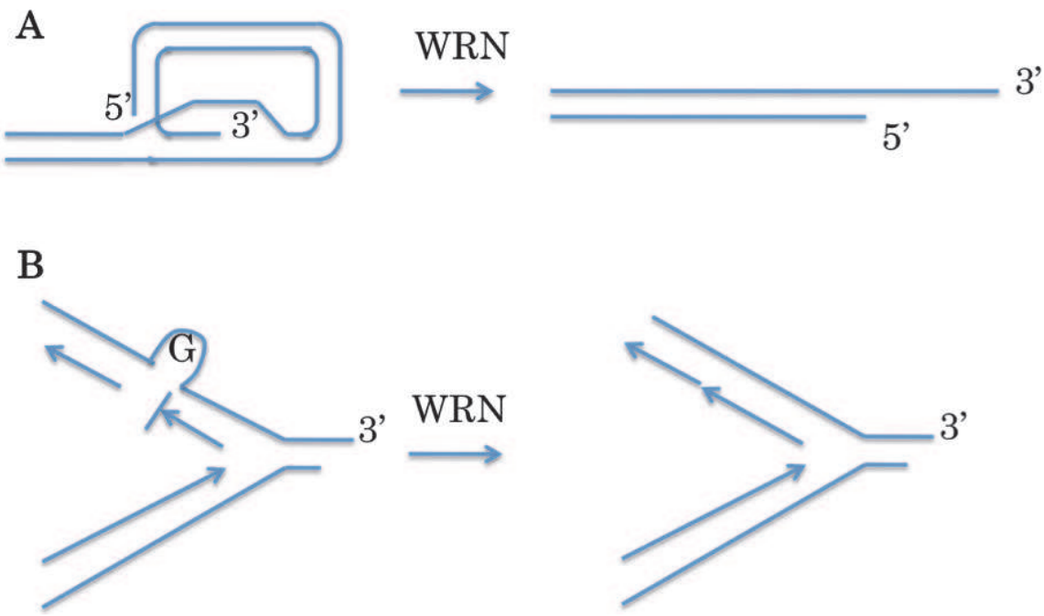

Fig. 3. WRN activities on a telomeric D-loop structure (A) and on a lagging strand telomere (B) during S phase. **A**. The model shows that WRN helicase releases the invading strand during S phase. **B**. WRN resolves G-quartet (G) formed on the lagging telomeric DNA.

inhibition of WRN and POT1 also lender human cells sensitive to anti-microtubule drug vinblastine, implying the functional conservation between human POT1 and WRN and *S. pombe* Pot1 and Rqh1(Takahashi et al. 2011). The other double knockdown experiments of WRN and POT1 in human cells show that human POT1 is required for efficient telomere C-rich strand replication in the absence of WRN (Arnoult et al. 2009). The functional interaction between human POT1 and RecQ helicase WRN is also suggested by in vitro experiment. Purified human POT1 binds to WRN and POT1 binding on telomeric DNA regulates the unwinding activity of WRN (Opresko et al. 2005; Sowd, Lei, and Opresko 2008; Opresko, Sowd, and Wang 2009). Based on these and other data, several possible roles of WRN at telomere are suggested (Rossi, Ghosh, and Bohr 2010) (Fig. 3). Telomere is capped by telomere binding proteins called shelterin and the chromosome end is protected through strand invasion of the duplex telomeric repeat by the 3′ single-stranded overhangs, which is called t-loop (Palm and de Lange 2008). As WRN acts to release the 3′ invading tail from a telomeric D loop in vitro, WRN may be involved in the regulation of the t-loop (Opresko et al. 2004). Single-stranded overhangs can fold into G-quadruplex DNA, which may inhibit DNA polymerase and telomerase at telomere (Zaug, Podell, and Cech 2005). Therefore, WRN may disrupt telomeric G-quadruplex with POT1 to facilitate DNA replication and/or telomere elongation at telomeres.

4. Roles of RPA in telomere maintenance

Replication protein A (RPA) is a heterotrimeric single-stranded non-specific DNA-binding protein consisting of a large (70 kDa), middle (32 kDa) and small (14 kDa) subunit. RPA is conserved from yeast to human and is essential for DNA replication, repair, and recombination (Binz, Sheehan, and Wold 2004). The large subunits of RPA in human, *S, cerevisiae* and *S. pombe* are named as RPA70, Rfa1 and Rad11, respectively. RPA is involved in HR repair by binding the single-stranded DNA generated by DNA end-processing at DSB ends. Single-stranded DNA is also produced at telomere. But RPA is suggested to be excluded from single-stranded telomere overhangs because it will lead to DNA damage checkpoint activation and cell cycle arrest. However, genetic evidences suggest the role of RPA in telomere maintenance. In this section, possible roles of RPA in telomere maintenance will be discussed. The functional relationship between RPA, RecQ helicase, and Taz1 will be also discussed.

4.1 Roles of RPA in DNA repair

Mutations in *S, cerevisiare rfa1* lender cells to sensitive to DNA damage and affect recombination efficiency, suggesting the involvement of RPA in recombination and repair processes (Smith and Rothstein 1995; Firmenich, Elias-Arnanz, and Berg 1995; Umezu et al. 1998). *S. pombe rad11* mutants are also sensitive to DNA damage and *rad11-D223Y* mutant is epitatic to *rad50* mutant, suggesting that RPA is involved in the HR repair (Parker et al. 1997; Ono et al. 2003). The roles of RPA in HR repair is well studied by in vitro system using *S. pombe* proteins (Kurokawa et al. 2008; Murayama et al. 2008). These in vitro and other genetic studies suggest that RPA binds to the single-stranded DNA generated by processing at DSB end. Then Rad22 (the *S. pombe* Rad52 homolog) helps Rad51 to displace RPA from single-stranded DNA. RPA bound to the single-stranded DNA recruits DNA damage checkpoint proteins to the DSB site to activate DNA damage checkpoint (Zou and Elledge 2003).

4.2 Roles of RPA in telomere maintenance

Telomere ends have single-strand overhangs, which may serve substrates for RPA. However, it is belieaved that RPA is excluded from telomere to suppress DNA damage checkpoint activation at telomere. Indeed, binding of human and mouse POT1 to telomeric ssDNA inhibits the localization of RPA to telomeres (Barrientos et al. 2008) (Gong and de Lange 2010). However, there are several genetic evidences suggesting that RPA is involved in telomere maintenance. Mutation of *S. cerevisiae RFA1* gene, *rfa1-D228Y* in *Yku70* mutant background causes telomere shortening, demonstration that RPA is required for telomere length regulation at dysfunctional telomere (Smith, Zou, and Rothstein 2000). Moreover, certain mutant alleles of *RFA2* gene, encoding the middle subunit of RPA, in wild-type background causes telomere shortening, demonstration that RPA is required for telomere length regulation (Mallory et al. 2003). In addition, *S. cerevisiae* RPA binds to telomere especially in S phase and cells expressing truncated Rfa2 show impaired binding of the Est1, a component of telomerase (Schramke et al. 2004). Based on these data, they proposed that RPA activates telomerase by loading Est1 onto telomeres during S phase. *S. pombe rad11-D223Y* mutant, which corresponds to the *S.cerevisiae rfa1-D228Y* mutant, has short telomere in wild-type background. Moreover, *S. pombe* RPA binds to telomere especially in S phase (Ono et al. 2003; Moser et al. 2009). A genome-wide screen for *S. pombe* deletion mutants shows that deletion of *ssb3*, the small subunit of RPA, affects telomere length(Liu et al. 2010). These facts suggest that RPA plays important role in telomere maintenance in both *S. cerevisiae* and *S. pombe*. Human RPA is also enriched at telomere during S phase, possibly due to exposure of single-stranded DNA during telomere replication (Verdun and Karlseder 2006). The aspartic acid at position 223 in *S. pombe* Rad11 is important for telomere length regulation, which corresponds to the position 227 in human RPA70 (Ono et al. 2003). Similarly, expression of RPA70-D227Y mutant protein in human fibrosarcoma HT1080 cells causes telomere shortening, suggesting that human RPA also plays role in telomere length regulation (Kobayashi et al. 2010). Possible role of RPA at telomere is the regulation of the processing of telomere ends by controlling accessibility of DNA repair proteins and/or Pot1 to single-stranded overhang (Fig. 4).

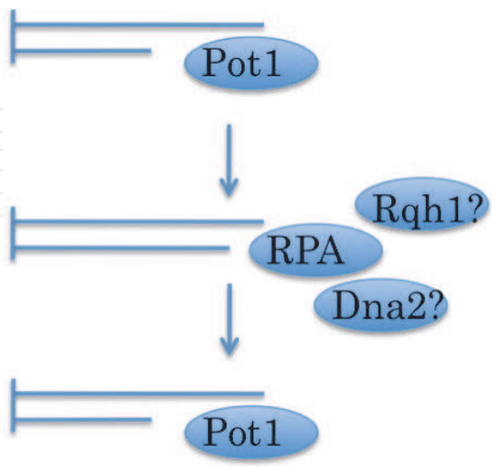

Fig. 4. The model shows that *S. pombe* RPA regulates the localizations and/or activities of proteins involved in the telomere maintenance. RPA may regulate Dna2 and/or Rqh1 during S phase.

4.3 Functional interaction between *S. pombe* Taz1, RPA and RecQ helicase

S. pombe taz1 rad11-D223Y double mutant lose telomere very rapidly, demonstrating that Taz1 and RPA collaborate to maintain telomere (Kibe et al. 2007). This rapid telomere loss can be suppressed by overexpression of Pot1. One possible explanation for this data is that Taz1 and RPA are required for the function of Pot1 at telomere and overexpression of Pot1 can rescue this defect. The rapid telomere loss of *taz1 rad11-D223Y* double mutant can be also suppressed by deletion of *rqh1*. Sgs1 is involved in the processing of telomere ends in *S. cerevisiae*. Similarly, *S. pombe* Rqh1 may be involved in the rapid telomere loss, possible by degradation of C-rich strand in *taz1 rad11-D223Y* double mutant (Fig. 5). The other functional relationship between Taz1 and Rqh1 is reported by Cooper group. *taz1* disruptant is sensitive to low temperature (Miller and Cooper 2003). Telomere entanglement is suggested to be a reason for this cold sensitivity. They found that unsumoylated Rqh1 mutant can suppress this cold sensitivity (Rog et al. 2009). Trt1 is a catalitic subunit of telomerase in *S. pombe*. *trt1* single mutant loses telomeric DNA gradually (Nakamura, Cooper, and Cech 1998). In contrast, *taz1 trt1* double mutant lose telomere very rapidly (Miller, Rog, and Cooper 2006). The replication fork stalling at the telomeres and resultant DSB is suggested to be a season for the rapid telomere loss in *taz1 trt1* double mutant. Unsumoylated Rqh1 mutant can also suppress this rapid telomere loss. Based on these data, they propose that sumoylated Rqh1 promotes telomere breakage and entanglement in *taz1* disruptant. This data demonstrate that the activity of Rqh1 at telomere is regulated to protect telomere. However, it remains unclear how Rqh1 and other DNA repair proteins are regulated at telomere. The functional interactions between human TRF1/TRF2 (*S. pombe*

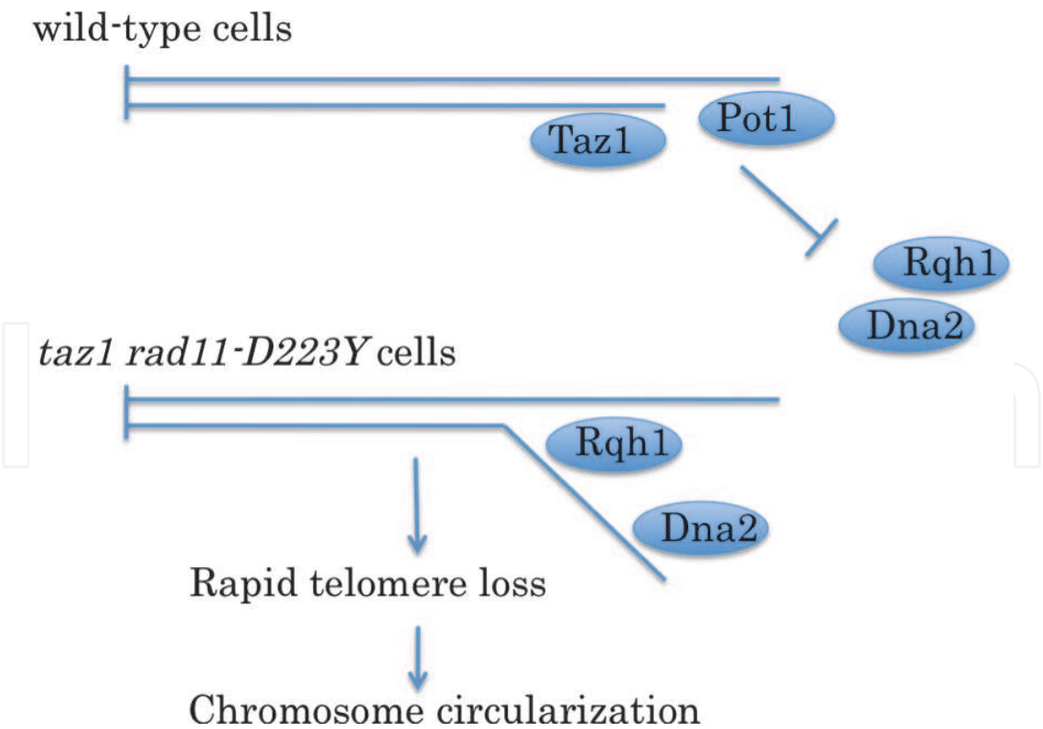

Fig. 5. The model shows that *S. pombe* Taz1 and RPA are required for prevent rapid telomere loss. In *taz1 rad11-D223Y* double mutant, Pot1 can not function properly and Rqh1 and possibly Dna2 resects telomere ends, which causes rapid telomere loss.

Taz1 ortholog) and human RecQ homolog WRN and BLM in telomere maintenance are also suggested (Opresko 2008). TRF2 interacts with WRN and stimulates helicase activity of WRN in vitro (Opresko et al. 2002; Machwe, Xiao, and Orren 2004). Expression of a TRF2 lacking the amino terminal basic domain induces the telomeric circle formations and rapid telomere deletions (Wang, Smogorzewska, and de Lange 2004). These events are dependent on WRN (Li et al. 2008). TRF2 also protects the displacement of Holliday junctions with telomeric arm by WRN in vitro (Nora, Buncher, and Opresko 2010). These facts suggest that the regulation of WRN activity by TRF2 is required to protect telomere.

5. Conclusion

This chapter focused on the roles of proteins involved in the processing of DBS ends at functional and dysfunctional telomere in *S. pombe, S. cerevisiae* and human. We found that MRN, Dna2, and possibly RecQ helicase Rqh1 are involved in the processing at telomere ends in *S. pombe*. Lydall group and other group found that Exo1, RecQ helicase Sgs1, Dna2, and Pif1 are involved in the processing at telomere ends in *S. cerevisiae*. Interestingly, most of these proteins were also involved in the processing of DNA double-strand break ends. These facts raise a new question of how these proteins are regulated at telomere ends. This chapter also focused on the functional interactions between telomere capping proteins and proteins involved in the processing of DBS ends mainly in *S. pombe*. We found that Taz1 and RPA collaborate to inhibit DNA end-processing, possibly by RecQ helicase, to prevent telomere loss. We also found that single-stranded telomere-binding protein Pot1 and RecQ helicase Rqh1 collaborate to inhibit homologous recombination at telomere. Cooper group found that RecQ helicase Rqh1 makes *taz1* disruptant sensitive to cold temperature by creating telomere entanglement. From these analyses, we learned that both double-stranded and single-stranded telomere binding proteins play critical roles to control proteins involved in DNA repair at chromosome ends.

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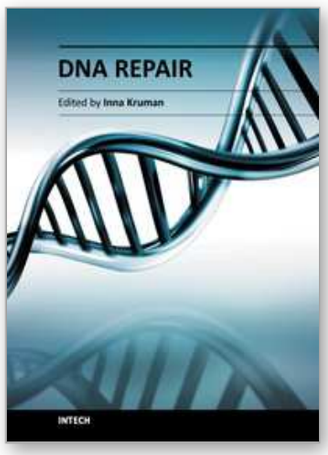

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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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