Supplemental Information

Telomerase Activation

after Recruitment in Fission Yeast

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Armstrong Figure S1, Related to Figure 1

DNA Size Standard

Sp. est1 mRNA

TER1

GAD-ccq1

BRL-est1-TER1

+ RT - RT + RT - RT + RT - RT

wt genomic DNA control

αFlag

αCdc2

+ M - M

- M

10 kb

8 kb

6 kb

5 kb

4 kb

3 kb

2.5 kb

2 kb

1.5 kb

1 kb

0.6 kb

0.4 kb

0.2 kb

2.5 kb

EcoR1 Apa1

- 2.5 kb

- 2.5 kb

0.4 kb

0.2 kb
A

**Pot1-BD (155-213)**

**Ccq1 BD (422-490)**

**Tpz1 truncations**

| T7 | Full length | 1-421 | 1-213 | 1-193 | 155-508 | 422-508 | 479-508 | 422-490 | 155-213 |
|----|-------------|-------|-------|-------|---------|---------|---------|---------|---------|
| T7 | Poz1        | +His  | +Ade  |       |         |         |         |         |         |
| T7 | Ccq1        |       |       |       |         |         |         |         |         |
| T7 | Pot1        |       |       |       |         |         |         |         |         |

**Activation Domain**

**Pot1**

B

Armstrong Figure S3, Related to Figure 3
A

Parental Diploid

trt1+/trt1-tpz1
tpz1+/tpz1Δ

trt1-tpz1
tpz1+

Haploid Offspring

trt1-tpz1
tpz1Δ

OR

Parental Diploid Haploid Offspring

Ptrt1
ccq1

Ttrt1

Ptrt1 Ttrt1

Ttrt1

ccq1tpz1

Δ

no tag

tpz1-PK

trt1-PKtrt1-tpz1  tpz1+
tpz1∆

trt1-tpz1(K75A)
trt1-tpz1(L449A)

α
PK

αCdc2

B

tpz1Δ

kDa:

no tag

tpz1-PK

trt1-PK

trt1-tpz1

trt1-tpz1(L449A)

trt1-tpz1(K75A)

αPK

αCdc2

C

1. recruitment

2. remodeling

3. activation

Pot1

Tpz1

Ccq1

Trt1

TER1

Est1

TER1

Est1

TER1

Est1

TER1
Supplemental Information Legends:

Figure S1. Expression studies (Related to Figure 1)

A. Expression of gene products in yeast three hybrid assay. Western blot showing inducible expression of 3xFlag-Tpz1 from the MET promoter. Protein was extracted from cells at the time of plating, after growth in the presence or absence of methionine (+M or –M respectively), and subjected to SDS-PAGE. Anti-Flag was used to detect Tpz1 protein. Anti-Cdc2 was used as a control for loading.

B. Check for inducible expression of TER1 from the MET promoter in yeast three hybrid assay. RNA extracted from cells at the time of plating, after growth in the presence or absence of methionine (+M or –M respectively), was subjected to RT-PCR for TER1. PCR products were visualised on a 2% agarose gel. As a control, the RT enzyme was substituted with water (-RT). RT-PCR of EST1 mRNA was carried out as a control.

C. Tpz1 over-expression activates telomerase. Telomere Southern blot of genomic DNA from cells grown in the presence (OFF condition) or absence (ON condition) of thiamine, which represses expression from the nmt41 promoter. DNA was normalized, digested with EcoRI and hybridised with a telomeric probe.

D. Western blots comparing protein expression levels between the endogenous and nmt41 promoters for strains used in the Southern blots. WCEs were subjected to SDS-PAGE and hybridised with anti-PK and anti-Flag antibodies. Anti-Cdc2 was used as a control for loading of total protein.

E. Telomere Southern blot of genomic DNA from cells grown in the absence of thiamine to over-express Tpz1-3xFlag from the nmt41 promoter. DNA was
normalized, digested with EcoRI (left of blot) or Apal (right of blot) and hybridised with a telomeric probe. In wild type, size of EcoRI and Apal telomere fragments is approximately 1kb and 0.3kb, respectively.

**Figure S2. Protein expression and telomere length in tpz1 OB-fold mutants (Related to Figure 2)**

A. Western blot showing expression levels of Tpz1 OB-fold mutant proteins in heterozygous diploid strains. Slower migrating forms were observed in some of the mutants.

B. Telomere Southern blot of heterozygous diploid strains. DNA was normalized, digested with EcoRI and hybridised with a telomeric probe.

C. Telomere Southern blot of Tpz1 OB-fold haploid mutant strains. DNA was normalized, digested with EcoRI and hybridised with a telomeric probe.

**Figure S3. Mutation of the OB fold does not affect shelterin formation or function (Related to Figure 3)**

A. Yeast-2-hybrid analysis: the OB fold domain of Tpz1 (residues 1-154) is not required for Poz1, Ccq1 or Pot1 interaction. A diagram depicting the series of truncations of Tpz1 is shown in the upper panel. Equal amounts of cells were spotted on selection plates (-His -Ade) and a non-selective control plate for cell growth (+His +Ade).

B. Tpz1-K75A reduces telomerase activity in a manner independent of the Taz1 complex. Telomere Southern blot of genomic DNA normalized, digested with EcoRI and hybridized with a telomeric probe.
Figure S4. The fusion system and hypothetical model of telomerase recruitment and activation (Related to Figure 4)

A. Schematic diagram of the fusion system. The *tpz1* gene sequence with nine tandem PK sequences was inserted between the gene body and terminator of one *trt1* allele in a diploid strain heterozygous for *tpz1Δ*. Expression of the intact chimera gene product (Trt1-9xPK-Tpz1) through the endogenous *trt1* promoter was confirmed using anti-PK antibody (Figure S6). After sporulation, haploids were obtained which expressed the fusion protein from the *trt1* locus in a *tpz1Δ* or *tpz1+* background.

B. Western blot showing expression levels of PK-tagged Tpz1 and Trt1 proteins and the chimeric Trt1-Tpz1 fusion product. Anti-Cdc2 was used as a control for loading of total protein. * indicates a non-specific band recognised by the anti-PK antibody. Trt1-PK can be seen just above the non-specific band.

C. Hypothetical model of telomerase activation

1. Telomerase recruitment: Est1 navigates telomerase to telomeres bearing Ccq1 that has been phosphorylated by ATR [S1-S3].

2. Interaction of Est1 with Ccq1 releases Ccq1 and Est1 from the telomere and telomerase respectively (see also Figure 1).

3. Direct interaction of Tpz1 with Trt1 and re-association of Ccq1 are required for the activation of telomerase (Figures 1 and 4). How the Trt1 catalytic subunit physically binds to Tpz1 remains to be established.

Whilst Est1 guides telomerase to telomeres (1), Est1 tethered Trt1 does not seem to directly associate with telomeres. Rather, recruitment of Est1 appears to release Ccq1 from Tpz1, and also TER1 from Est1 (2). Such a
change in conformation may promote a stable interaction between the telomeres and Trt1, possibly with Tpz1 directly, thereby stimulating telomerase activity (3). Because both Ccq1 and Tpz1 can interact with Trt1 in a TER1-independent manner (Figure 1) and the Ccq1-Tpz1 association is required for telomere elongation when Trt1 is fused to Tpz1 (Figure 4), Ccq1 is likely to re-associate with Tpz1 after interaction with Est1, as is Est1 with TER1. The requirement for an altered conformation is potentially why Trt1 does not directly bind to Tpz1 without being guided to the telomere by Est1. However, activation of telomerase after recruitment does not occur solely through the “opening” of shelterin structure (Figure S1E). Rather a stable and direct interaction between Trt1 and Tpz1 is required for telomerase activity, as illustrated by the ability of our Trt1-Tpz1 fusion to rescue the telomerase activity defect caused by mutation of lysine 75 within the Tpz1 OB-fold (Figures 2 and 4). Further study is necessary to fully understand how Ccq1 and Tpz1 cooperate to promote telomerase activity.
| KTP strain | genotype |
|-----------|----------|
| 1         | \( h^+ \) |
| 1962      | \( h^+ \) leu1-32 ura4-D18 trt1-13xMyc:natMX6 |
| 2585      | \( h^+ \) leu1-32 ura4-D18 trt1-13xMyc:natMX6 ccq1-3xPK:hygMX6 |
| 489       | \( h^+ \) leu1-32 ura4-D18 tpz1-9xPK:kanMX6 |
| 2331      | \( h^+ \) leu1-32 ura4-D18 tpz1-9xPK:kanMX4 trt1-13xMyc:natMX6 |
| 2544      | \( h^+ \) est1-G5-9xPK:kanMX4 trt1-13xMyc:natMX6 |
| 803       | \( h^+ \) ade6-M210 ccq1-13xMyc:natMX6 |
| 2101      | \( h^+ h^+ \) ade6-M210/M216 |
| 1486      | \( h^+ \) ade6-M? leu1-32 ura4-D18 his3-D1 ccq1::ura4^+ |
| 1938      | \( h^+ \) ade6-M216 tpz1-3xHA:kanMX6 |
| 2360      | \( h^+ \) ade6-M210 tpz1(K75A)-3xHA:kanMX6 |
| 2381      | \( h^? \) ade6-M? tpz1(K75R)-3xHA:kanMX6 |
| 2382      | \( h^+ \) ade6-M? tpz1(T78A)-3xHA:kanMX6 |
| 2800      | \( h^+ \) ade6-M? tpz1(T78D)-3xHA:kanMX6 |
| 2791      | \( h^+ \) ade6-M? tpz1(T78E)-3xHA:kanMX6 |
| 2833      | \( h^? \) ade6-M? tpz1(K75A,T78A)-3xHA:kanMX6 |
| 2103      | \( h^+ h^+ \) ade6-M210/M216 trt1::hygMX6/+ |
| 1747      | \( h^+ \) ade6-M? tpz1::kanMX6 |
| 1743      | \( h^+ h^+ \) ade6-M210/M216 tpz1(K75A)-3xHA:kanMX6/+ |
| 2465      | \( h^+ \) ade6-M? trt1::hygMX6 |
| 2569      | \( h^+ \) ade6-M216 tpz1-3xHA:kanMX6 trt1::natMX6 |
| 2571      | \( h^+ \) ade6-M210 tpz1(K75A)-3xHA:kanMX6 trt1::natMX6 |
| 1889      | \( h^+ \) ade6-M? ccq1(T93A)-3xflag:natMX6 |
| 2662      | \( h^+ \) ade6-M216 leu1-32 ura4-D18 his3-D1 tpz1(K75A)-3xHA:kanMX6 ccq1(T93A)-3xflag:natMX6 |
| 600       | \( h^+ \) ura4-D18 poz1::natMX6 |
| 604       | \( h^+ \) leu1-32 ura4-D18 rap1::natMX6 |
| 209       | \( h^+ \) ade6-M210 leu1-32 ura4-D18 his3-D1 taz1::hygMX6 |
| 2514      | \( h^+ \) ade6-M210 poz1::natMX6 tpz1(K75A)-3xHA:kanMX6 |
| 2515      | \( h^+ \) ade6-M210 leu1-32 ura4-D18 his3-D1 rap1::natMX6 tpz1(K75A)-3xHA:kanMX6 |
| 2401      | \( h^+ \) ade6-M210 leu1-32 taz1::hygMX6 tpz1(K75A)-3xHA:kanMX6 |
| 1628      | \( h^+ \) ade6-M210 trt1-9xPK:kanMX6 |
| 2570      | \( h^+ \) ade6-M216 tpz1-3xHA:kanMX6 trt1-9xPK:natMX6 |
| 2594      | \( h^+ \) ade6-M? tpz1(K75A)-3xHA:kanMX6 trt1-9xPK:natMX6 |
| 2655      | \( h^+ \) trt1-9xPK:natMX6 ccq1-3xflag:hygMX6 tpz1-3xHA:kanMX6 |
| 2657      | \( h^+ \) trt1-9xPK:natMX6 ccq1-3xflag:hygMX6 tpz1(K75A)-3xHA:kanMX6 |
| 1989      | \( h^+ h^+ \) ade6-M210/M216 tpz1::kanMX6/+ trt1-9xPK-tpz1:natMX6/+ |
| 1990      | \( h^+ \) ade6-M210 trt1-9xPK-tpz1:natMX6 |
| 1993      | \( h^+ \) ade6-M216 tpz1::kanMX6 trt1-9xPK-tpz1::natMX6 |
| 2870      | \( h^+ \) ade6-M216 tpz1::neoCV trt1-9xPK-tpz1::natMX6 |
| 2873      | \( h^+ \) ade6-M216 tpz1::hygMV trt1::trt1-9xPK-tpz1::natMX6 |
| 2871      | \( h^+ \) tpz1::neoCV trt1-9xPK-Tpz1(K75A)::natMX6 |
| 2905      | \( h^+ \) ade6-M216 trt1-9xPK-Tpz1::natMX6 ccq1(T93A)-3xflag:natMX6 |
| 3058      | \( h^+ \) ade6-M216 tpz1::neoCV trt1-9xPK-tpz1::natMX6 ccq1::hygMV |
| KTP strain | genotype |
|------------|----------|
| 2875       | h^ tpz1::hygMV trt1-9xPK-Tpz1(L449A):natMX6 |
| 2267       | h^ ccq1-3xflag:natMX6 |
| 1382       | h^ ccq1-3xPK:hyg:MX6 |
| 751        | h^ leu1-32 ura4-D18 tpz1-3xflag:ura4^ |
| 1701       | h^ leu1-32 ura4-D18 tpz1::kanMX6:P^{nmt41}>tpz1-3xflag:ura4^ |
| 295        | h^^{nmt41} leu1-32 ura4-D18 est1::hygMX6:P^{estf1}>18xPK-est1 |
| 1521       | h^ est1::kanMX6:P^{nmt41}>18xPK-est1 |
| 1561       | h^ leu1-32 ura4-D18 trt1::ura4^:P^{nmt41}>trt1^ |
| 1509       | h^ ade6-M210 leu1-32 ura4-D18 trt1::ura4^:P^{nmt41}>trt1-9xPK:kanMX6 |
| 2398       | h^ ura4-D18 poz1::natMX6 tpz1::kanMX6:P^{nmt41}>tpz1-3xflag:ura4^ |
| 1725       | h^/h^ ade6-M210/M216 tpz1::kanMX6/+ |
| 1798       | h^/h^ ade6-M210/M216 tpz1-3xHA:kanMX6/+ |
| 1882       | h^/h^ ade6-M210/M216 tpz1(EKRI74AAAA)-3xHA:kanMX6/+ |
| 1742       | h^/h^ ade6-M210/M216 tpz1(E74A)-3xHA:kanMX6/+ |
| 1744       | h^/h^ ade6-M210/M216 tpz1(R76A)-3xHA:kanMX6/+ |
| 2471       | h^/h^ ade6-M210/M216 tpz1(I77A)-3xHA:kanMX6/+ |
| 2364       | h^/h^ ade6-M210/M216 tpz1(TS78AA)-3xHA:kanMX6/+ |
| 2363       | h^/h^ ade6-M210/M216 tpz1(T789A)-3xHA:kanMX6/+ |
| 1745       | h^/h^ ade6-M210/M216 tpz1(S79A)-3xHA:kanMX6/+ |
| 1969       | h^ ade6-M? tpz1(EKRI74AAAA)-3xHA:kanMX6 |
| 2359       | h^ ade6-M? tpz1(E74A)-3xHA:kanMX6 |
| 2470       | h^ ade6-M? tpz1(R76A)-3xHA:kanMX6 |
| 2495       | h^ ade6-M? tpz1(I77A)-3xHA:kanMX6 |
| 2383       | h^ ade6-M? tpz1(TS78AA)-3xHA:kanMX6 |
| 2361       | h^ ade6-M? tpz1(S79A)-3xHA:kanMX6 |
| 2945       | h^ ade6-M? trt1::trt1-9xPK-tpz1:natMX6 ccq1(T93A)-3xflag: natMX6 tpz1::neoCV |
| 2946       | h^ ade6-M216 trt1::trt1-9xPK-tpz1:natMX6 ccq1(T93A)-3xflag: natMX6 tpz1::neoCV |

Use of “$P^{nmt41}$” before a gene indicates the gene is expressed from the $nmt41$ promoter rather than its endogenous promoter.
Supplemental Experimental Procedures:

Yeast genetics and plasmids for strain construction

All of the strains used for this study are listed in Table S1. All media and supplements were purchased from FORMEDIUM™. Fission yeast were grown at 32°C in standard rich media (YES) unless indicated. Transcription using the nmt41 promoter was induced by culturing cells in the absence of Thiamine in Edinburgh Minimal Media (EMM). Budding yeast for yeast two (three) hybrid system (Matchmaker® Gold Yeast Two-Hybrid System, Clontech), Y2H Gold, were grown in Synthetic Defined (SD) media with indicated drop-out supplements at 25°C.

Gene deletion and tag insertion at the C-terminus were described previously [S4]. Details of strains harbouring Est1-G5-9xPK (or V₅), Trt1-9xPK (or V₅), Trt1-13xMyc and Ccq1-3xflag were described previously [S4, S5]. The C-terminus tagging of Tpz1 and the N-terminus tagging of Est1 do not affect telomere length (see telomere length in main figures).

A plasmid for N-tag Est1 was constructed by cloning the est1 gene including 1100 bases of the upstream and 300 bases of the downstream regions. The start codon of est1⁺ was replaced with 13xMyc or 12xPK sequences. A hygMX6 cassette was inserted at the 3’ UTR of the upstream gene rhp23⁺.

For Trt1-Tpz1 fusion, the C-terminus region of the trt1⁺ gene (from BamHI site in the gene), 9xPK C-terminus tags, adh1⁺ terminator and natMX6 cassette were cloned and assembled by subcloning, and tpz1⁺ cDNA was inserted between the PK tag and the stop codon. Resulting plasmid were digested with PacI (in trt1 gene) to insert the whole plasmid at the trt1⁺ gene locus. Expression of the fusion construct from the endogenous promoter was
confirmed by western blotting. To generate tpz1 point mutant cells, the tpz1+ gene including 800 bases of the upstream region was cloned into a 3xHA C-terminus tagging plasmid. All point mutations were generated by Quickchange lightning site-directed mutagenesis kit (Agilent Technologies). One tpz1 allele in a diploid strain was replaced by the HA tagged mutant tpz1 with a kanMX6 cassette.

**Protein extraction and immunoprecipitation**

Co-immunoprecipitation was as described previously [S4] with minor modifications. Monoclonal anti-Flag M2 antibody (Sigma), anti-PK antibody (AbD Serotec) or anti-HA antibody (Covance) was incubated with mouse IgG-coated Dynabeads (Life technology) overnight at 4°C and the beads were rinsed to remove excess antibodies. Logarithmically growing cells were harvested and frozen at −80°C. Pellets were resuspended in the same volume of HB2 buffer (50 mM HEPES/KOH at pH 7.5, 140 mM NaCl, 15 mM EGTA, 15 mM MgCl2, 0.1% NP-40, 0.5 mM Na3VO4) containing protease inhibitors (1 mM dithiothreitol, 1 mM PMSF, 0.1% Protein inhibitor cocktail set III (Sigma), 0.1 ng/mL MG132 (Sigma), 10 U/mL TURBO DNase (Ambion), 1 U/µL RNasin (Promega). Cells were broken using a Fast Prep machine (Thermo), briefly sonicated by Biorupter and centrifuged to harvest the chromatin containing cell extract. Whole cell extract (WCE) was incubated with the pre-coated beads for one hour at 4°C. After extensive washing, the beads were resuspended in SDS loading buffer, boiled, and subjected to western blotting with anti-Flag M2, anti-HA, anti-PK or anti-Myc 9E11 (Cell Signaling). Anti-Cdc2 (Santa Cruz) and anti-Histone H3 (Abcam) were used to
control for input and telomere-IP specificity, respectively. To remove RNA from the complex, 1% RNase Cocktail™ [50 U/ml RNaseA and 200 U/ml RNaseT1] (Ambion) was added during the immunoprecipitation and washing step. Removal of RNA was confirmed by RT-PCR.

**Reverse Transcriptase PCR (RT-PCR)**

Detection of RNA was conducted according to the Maxima Reverse Transcriptase manual (Thermo Scientific). RT-PCR for TER1 was performed using primer 5’-GATCCATGGATCTCACGTAATG-3’ for RT and a primer set 5’-CAGTGTACGTGAGTCTTCTGCTTT-3’ and 5’-CAAAAATTCGTTGTGATCTGACAAGC-3’ for PCR [S6]. RT-PCR for est1 mRNA was performed using primer 5’-GAGGCAAGTAGAAGAATATCTGG-3’ for RT and a primer set 5’-ATACATCCTCGACACGTTGGT-3’ and 5’-CAATTATACACGCATTCTAATGCCTC-3’ for PCR. PCR products were visualised in 2% agarose gel.

**Telomere Southern blotting**

Telomere Southern blotting was performed as described previously [S4]. Genomic DNA for Southern blot was prepared 2 weeks after generation of the strains unless indicated. Equal amounts of EcoRI digested DNA fragments were separated on a 1% agarose gel and subjected to Southern blotting with a telomere probe.
Chromatin Immunoprecipitation (ChIP)

Trt1 ChIP was performed as described previously [S4]. For ChIP efficiency, precipitated DNA was quantified using qPCR (SyberGreen and LightCycler 480, Roche) with a primer set 5’- CAGTGACGTAGTCTTCTGCTT-3’ and 5’- CAAAATTCGTTGATCTGACAAGC-3’ for the telomeres and a primer set 5’-GGATTCCTACGTGTTGATGATGA-3’ and 5’-GGAGGAAGATTGACGACGATGATA-3’ for the internal control act1. Enrichment of Trt1 bound telomeres was calculated after normalising to act1 (telo/act1). The efficiency of Trt1 binding to telomeres was expressed as the fold enrichment compared with the value obtained from cross-linked wild-type cells harbouring untagged protein. Trt1 ChIP in tpz1-K75A was performed using an early generation strain harvested soon after sporulation from the heterozygous diploid, which contains long enough telomeres for the assay. DNA was not enriched by Trt1 immunoprecipitation under non-cross-linked conditions (data not shown).

Yeast two (three) hybrid assay

The assay was conducted according to the Matchmaker gold yeast two hybrid system manual (Clontech). Expression vectors for the GAL binding domain (BD) fused proteins and the GAL activation domain (AD) fused proteins were generated by subcloning of the indicated cDNAs into pGBK and pGAD, respectively. Expression of BD and AD fused proteins were confirmed by Western blotting using anti-myc and anti-HA antibodies, respectively. To perform yeast three hybrid assay, a pBRL vector (home made pBridge (Clontech) -Like vector) that expresses both the BD-fused protein and the
third factor, was constructed as follows. Briefly, the budding yeast MET17 promoter (500 bases upstream region of the MET17 gene), the fission yeast ter1+ gene and the budding yeast ADH1 terminator (210 bases downstream region of the ADH1 gene) were cloned and assembled by subcloning. The resulting MET17 regulated ter1+ cassette was inserted after, but in the same orientation as, the BD expression cassette at the AvrII site of the pGBK vector to express TER1 non-coding RNA (pBRL-est1-ter1). To express the Tpz1 protein as the third factor, the ter1+ gene in the pBRL-est1-ter1 vector was replaced with a chimera gene containing three tandem flag tags, the nuclear localisation signal coding sequence and tpz1+ cDNA (pBRL-est1-tpz1). Expression of the third factor (TER1 or 3xFlag-nls-Tpz1) in the absence of methionine was confirmed by RT-PCR for TER1 or western blotting with anti-flag antibody for Tpz1 (Figure S1).
Supplemental References:

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S3. Moser, B.A., Chang, Y.T., Kosti, J., and Nakamura, T.M. (2011). Tel1ATM and Rad3ATR kinases promote Ccq1-Est1 interaction to maintain telomeres in fission yeast. Nature structural & molecular biology 18, 1408-1413.

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S6. Moser, B.A., Subramanian, L., Khair, L., Chang, Y.T., and Nakamura, T.M. (2009). Fission yeast Tel1(ATM) and Rad3(ATR) promote telomere protection and telomerase recruitment. PLoS genetics 5, e1000622.