Two Independent Regions of Human Telomerase Reverse Transcriptase Are Important for Its Oligomerization and Telomerase Activity*

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Human telomerase reverse transcriptase (hTERT), the catalytic subunit of telomerase, contains motifs conserved among reverse transcriptases. Several nucleic acid-dependent polymersases that share a “fingers, palm, and thumb substructure” were shown to oligomerize. Here we demonstrate that hTERT also has this ability using partially purified recombinant hTERTs and mammalian cells co-expressing differently tagged hTERTs. Human template RNA (hTR), by contrast, has no effect on the structural oligomerization of hTERTs. Therefore, hTERT has an intrinsic ability of oligomerization in the absence of hTR. We identified two separate regions as essential for the oligomerization. The regions, amino acids 301–538 (amino-terminal region) and amino acids 914–928 (carboxyl-terminal region), are outside the fingers and palm substructure covering motif T to D and interact with each other in vivo. A substituted mutant of hTERT, hTERT-D712A-V713I, which was reported as a dominant negative form of hTERT, bound to the wild-type hTERT and inhibited its telomerase activity transiently expressed in telomerase-negative finite normal human fibroblast. The truncated forms of hTERT containing the binding region to the wild-type hTERT partially inhibited the telomerase activity, probably by preventing the wild-type hTERT from forming an oligomer. Taken together, the oligomerization of hTERT is an important step for telomerase activity.

Telomeres are specialized structures positioned at the ends of linear eukaryotic chromosomes that provide a mechanism for maintaining chromosome length and stability. The termini of telomeric DNA cannot be fully replicated by the conventional replication machinery. Telomerase, a ribonucleoprotein complex composed of template RNA and several proteins, elongates telomeres as one means of end replication (1). Telomerase reverse transcriptase (TERT)1, the catalytic subunit of telomerase, is a specific type of reverse transcriptase that forms stable complexes with template RNA (TR) (2). Human TERT is the rate-limiting factor for telomerase activity both biologically and biochemically (3, 4). Introduction of hTERT into normal human primary cells overcomes senescence and extends their lifespan (3, 5). We recently reported that hTERT and hTR, are the minimum components required for telomerase activity reconstituted in vitro with purified forms (4).

TERT is part of a large family of nucleic acid-dependent nucleic acids polymersases that share a “fingers, palm, and thumb substructure” (2, 6–8). Human TERT contains several motifs conserved among many reverse transcriptases, and additional motifs conserved only among TERTs from species ranging from budding yeasts to humans (9–11). Some polymersases that share a fingers, palm, and thumb substructure, such as HIV reverse transcriptase, polio RNA-dependent RNA polymerases (RdRP), and hepatitis C virus RdRP, oligomerize (12–16). Oligomerization in these enzymes induces conformational changes, which provide active or open forms that are essential for catalytic functions.

In Saccharomyces cerevisiae, telomerase forms an active multimer in vivo that may contain two active sites. This suggests that Est2p can oligomerize (17). Recently, one group reported that the human telomerase complex also forms a homodimer that contains two template RNA molecules (18), and another group found that two separate, catalytically inactive TERT proteins can complement each other in trans to reconstitute catalytic activity (19). These results indicated that just one hTERT molecule and one hTR molecule alone could not reconstitute telomerase activity. In other words, hTERT and hTR molecules must form a multimer and reconstitute telomerase activity by working together. However, it was not clear whether disruptions to the oligomeric formation of hTERT reduce telomerase activity.

Here we demonstrate that two independent regions outside of motifs T to D have an important role in the oligomeric interaction of hTERT in vitro using purified recombinant hTERT in the absence of hTR, and in mammalian cells transiently co-expressing various tagged hTERTs. These two independent regions can interact. We also demonstrate that catalytically inactive truncated forms of hTERT, which contain the binding region can inhibit telomerase activity of the wild-type hTERT.

EXPERIMENTAL PROCEDURES

Plasmid Construction—Mammalian expression vectors: The plasmids pNKZ-FLAG, pNCZ-FLAG, and pNKZ-GST derived from pSG5UTPL, are mammalian expression vectors. pNKZ-FLAG or pNCZ-FLAG vector was used to express amino- or carboxyl-terminal FLAG-tagged protein. pNKZ-GST was used to express amino-terminal GST-fused protein (4, 20, 21).

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homologous recombination. To demonstrate that hTERT can oligomerize in vivo without template telomerase RNA, the lysate of COS-1 cells transiently co-transfected with HA-tagged hTERT and FLAG-tagged hTERT was treated with RNase A, and then the binding of FLAG-hTERT to HA-hTERT was examined by co-immunoprecipitation using anti-HA antibody. Although telomerase activity of cell extract was diminished by RNase treatment (Fig. 2B), RNase treatment had no effect on homologous interaction of hTERT (Fig. 2A), indicating that intact telomerase RNA is dispensable in the structural oligomerization of hTERT but absolutely necessary for telomerase activity.

Two Regions Bind to the Wild-type hTERT in Vitro and in Vivo—To examine the homologous interaction of hTERT, GST-fused and FLAG-tagged hTERT expressed in insect cells were purified using affinity chromatography (Fig. 1A, lanes 1–3), and the binding of FLAG-tagged hTERT to GST-hTERT was examined using the GST pull-down assay. Purified FLAG-hTERT was pulled-down by GST-hTERT in vitro (Fig. 1B, lane 5). This binding was specific, because GST alone could not bind FLAG-hTERT (Fig. 1B, lane 6). Importantly, the presence of human telomerase RNA (hTR) did not positively nor negatively affect this oligomeric interaction (Fig. 1C, lanes 7 and 8). We also confirmed that the oligomeric interaction occurred in vivo, because HA- and FLAG-tagged hTERT proteins transiently co-expressed in COS-1 cells were co-immunoprecipitated by anti-HA (Fig. 1D, lane 13) or by anti-FLAG M2 antibody (Fig. 1E, lane 20), respectively. These results indicate that hTERT proteins labeled with different tags interacted with each other in the oligomer form in vitro and in vivo. This interaction does not require hTR, strongly suggesting that hTERT has an intrinsic ability to oligomerize.

RNase Treatment Does Not Inhibit Homologous Interaction of hTERT in Vitro and in Vivo—To demonstrate that hTERT can oligomerize in vivo without template telomerase RNA, the lysate of COS-1 cells transiently co-transfected with HA-tagged hTERT and FLAG-tagged hTERT was treated with RNase A, and then the binding of FLAG-hTERT to HA-hTERT was examined by co-immunoprecipitation using anti-HA antibody. Although telomerase activity of cell extract was diminished by RNase treatment (Fig. 2A), RNase treatment had no effect on homologous interaction of hTERT (Fig. 2A), indicating that intact telomerase RNA is dispensable in the structural oligomerization of hTERT but absolutely necessary for telomerase activity.

Two Regions Bind to the Wild-type hTERT in Vitro and in Vivo—If the homonomic interaction of hTERT does not require the presence of hTERT, then the region(s) necessary for oligomeric interaction can be mapped using truncated forms of hTERT. Four truncations covering the amino-terminal region spanning...
the putative hTR-binding region (Fig. 3A, lanes 3, 4, 7, and 8), the carboxyl-terminal region harboring motif E, and the putative thumb domain (Fig. 3A, lanes 1, 2, 5, and 6), were constructed and the recombinant truncated proteins were purified from insect cells to examine the ability of these proteins to bind GST-hTERT by GST pull-down assay. Three constructs, CF1, NF1, and NF2, bound the wild-type GST-hTERT (Fig. 3B, lanes 11, 19, and 23), whereas CF2 had no binding ability \textit{in vitro} (Fig. 3B, lane 15). These results indicate that at least the amino- and carboxyl-terminal regions can bind the wild-type hTERT \textit{in vitro}. We then examined the binding abilities of the two regions \textit{in vivo} using truncated versions of FLAG-hTERT in the presence of HA-hTERT in COS-1 cells (Fig. 4A, lanes 2–11), as well as the ability of the expressed FLAG-hTERT
FIG. 3. Two regions can bind the wild-type hTERT in vitro. A, truncated forms of FLAG-tagged hTERT were expressed in insect cells, partially purified as described under “Experimental Procedures,” then analyzed by 12% SDS-PAGE and visualized by Coomassie Brilliant Blue staining (lanes 1–4) or subjected to Western blot analysis with anti-FLAG M2 antibody (lanes 5–8). Truncated proteins: lanes 1 and 5, CF1; 2 and 6, CF2; 3 and 7, NF1; 4 and 8, NF2. B, results of GST pull-down assay to evaluate for interaction of partially purified truncated FLAG-tagged hTERT with the wild-type GST-fused hTERT (lanes 9–12, interaction with FLAG-CF1; lanes 13–16, interaction with FLAG-CF2; lanes 17–20, interaction with FLAG-NF1; lanes 21–24, interaction with FLAG-NF2). GST-hTERT or GST, immobilized on glutathione beads, was incubated with each partially purified truncated FLAG-hTERT.

Bound proteins were fractionated by 12% SDS-PAGE then subjected to Western blot analysis with anti-FLAG M2 antibody.

The Amino- and Carboxyl-terminal Regions of hTERTs Interact in Vivo—The interactions between the two regions of hTERT and the wild-type hTERT raised two possibilities. The truncated regions may only bind to the wild-type hTERT as a partner, or they may interact with various forms of hTERT. We therefore examined whether these two binding regions interact with each other. Truncated forms of FLAG-hTERT and HA-hTERT were transiently co-expressed in COS-1 cells (Fig. 5A, lanes 1–5 and 11–15), then co-immunoprecipitated with anti-HA antibody. CF1, aa 914–1132, could bind NF2, aa 301–534, indicating that the truncated amino- and carboxyl-terminal regions interact with each other (Fig. 5A, lane 9). CF2, aa 928–1132, did not bind to any of the truncated proteins. These results strongly suggest that the amino acid sequence, aa 914–927 including motif E, is critical for the binding. Fig. 5 shows no interaction between the differently tagged amino- or carboxyl-terminal regions (Fig. 5A, lanes 6, 7, 16, and 17; other data not shown). Thus, the homomeric interaction does not require the wild-type hTERT but does require the amino- and carboxyl-terminal regions. The oligomeric interaction of hTERT proteins may proceed in a head-to-tail fashion, because the amino- and carboxyl-terminal regions bound each other but not the homologous regions. Under these conditions, NF1, aa 201–534, bound weakly to CF1 compared with NF2 (Fig. 5A, lane 8). The discrepancy may be due to the limitations of using truncation mutants the structural integrity of which may be disrupted.

hTERT-D712A-V713I and Two Truncation Mutants, CF1 and NF2, Partially Inhibited the Telomerase Activity—To estimate the functional relevance of oligomerization of hTERT for telomerase activity in mammalian cells, finite normal human fibroblasts, TIG-3 cells, were transfected with HA-tagged wild-type hTERT in combination with inactive substituted mutant of hTERT-D712A-V713I at the VDV sequence, which is critical for substrate binding, or several truncated versions of hTERT. Using the lysate of these transfected cells, telomerase activity was measured by TRAP assay and TRAP ELISA. The telomerase activity of the wild-type hTERT was clearly inhibited by hTERT-D712A-V713I in TIG-3 cells compared with that of the wild-type hTERT alone in the TRAP assay (Fig. 6B, lanes 7 and 11) and TRAP ELISA (Fig. 6C). In the TRAP ELISA, the telomerase activity of the wild-type hTERT in TIG-3 cells was partially reduced in combination with hTERT-CF1 or hTERT-NF2, which could bind the wild-type, compared with that in combination with vector or CF2, which could not (Fig. 6C). In the TRAP assay, these differences were not clear among the presence of different mutant hTERTs (Fig. 6B, lanes 7–10). However, in TRAP ELISA experiments, telomerase activity of the wild-type hTERT was inhibited by the truncated mutants in a dose-dependent manner (Fig. 6D). This result strongly suggests that the truncation mutants, which can bind to the wild-type hTERT, have a negative effect on telomerase activity.

DISCUSSION

TERT is a unique enzyme among a family of nucleic acid-dependent polymerases harboring a fingers, palm, and thumb substructure, because it forms a tight complex with template RNA for the activity (2, 10, 24). Its long amino- and carboxyl-terminal parts outside of the fingers and palm (aa 525–928) might retain TERT-specific functions (11, 22, 25–28), because these parts are somewhat conserved only among TERTs (9–11). We previously reported that hTERT and hTR are the minimal components required for telomerase activity when telomerase is reconstituted in vitro with two purified components (4). During this study we found that the catalytic activity of the purified hTERT was not detectable when concentrations of hTERT were low in the assay reaction (data not shown). This concentration dependence of hTERT reminded us of the template switching of telomerase previously reported in S. cerevi-
siae (17) and the oligomeric interactions of poliovirus (15) and hepatitis C virus RdRPs (29). Two groups recently reported the oligomeric role of telomerase using the different methods (18, 19). However, it was not clear whether TERT forms multimer intrinsically or with help of template RNA. Here we show that the homomeric interaction of hTERT in vitro with partially purified differently tagged-hTERTs. Human TR seems to have no effect on the structural oligomerization of hTERT (Fig. 1C), and RNase treatment did not affect the homomeric interaction in vivo (Fig. 2A) and in vitro (data not shown). These results

**Fig. 4. Two regions can bind the wild-type hTERT in vivo.** A, HA-tagged wild-type hTERT and the wild-type or truncated FLAG-tagged hTERT were transiently co-expressed in COS-1 cells. Cell extracts were immunoprecipitated with anti-HA antibody immobilized on protein A-Sepharose. Bound proteins were separated by 12% SDS-PAGE and subjected to Western blot analysis with anti-FLAG M2 (upper panels) or anti-HA antibodies (lower panels). Truncated proteins: lanes 2–11 and 13–22, HA-hTERT; 3 and 14, the wild-type FLAG-hTERT; 4 and 15, FLAG-CT1; 5 and 16, FLAG-CT2; 6 and 17, FLAG-NT; 7 and 18, FLAG-CF1; 8 and 19, FLAG-CF2; 9 and 20, FLAG-NF1; 10 and 21, FLAG-NF2; 11 and 22, FLAG-PF. Asterisks indicate specific bands for each the wild-type or truncated FLAG-hTERT protein. #, immunoglobulin chains. B, mapping of oligomeric interaction of hTERT by truncation analysis. TERT and truncations were drawn schematically. The motifs conserved within various reverse transcriptases are represented by boxes 1, 2, A, B, C, D, and E (22). The motif found specifically within TERT proteins is represented by box T (10).

**Fig. 5. Two binding regions interact in vivo.** HA-tagged truncated hTERT and truncated FLAG-tagged hTERT were co-expressed in COS-1 cells by transient transfection. Cell extracts were immunoprecipitated with anti-HA antibody immobilized on protein A-Sepharose. Bound proteins were fractionated by 12% SDS-PAGE and then subjected to Western blot analysis with anti-FLAG M2 (upper panels) or anti-HA antibodies (lower panels). Truncated proteins: lanes 1–10, HA-CF1; 11–20, HA-CF2; 1, 6, 11, and 16, FLAG-CF1; 2, 7, 12, and 17, FLAG-CF2; 3, 8, 13, and 18, FLAG-NF1; 4, 9, 14, and 19, FLAG-NF2. #, immunoglobulin chains.
indicate that hTERT has an intrinsic ability to oligomerize in the absence of intact hTR.

Two separate regions of hTERT (aa 301–538 and aa 914–1132) can be mapped to bind the wild-type hTERT in vitro and in vivo. This result may be consistent with a previous report (25) in which some combinations of two different truncated hTERT mutants defective in telomerase activity reconstituted telomerase activity. Two regions we mapped are outside the fingers and palm substructure covering motifs T to D. The amino-terminal fragment, aa 301–538, overlaps the region important for hTR binding (25, 26, 30). The carboxyl-terminal fragment, aa 914–1132, includes motif E and a putative thumb. The two separate regions can bind each other, but no homologous interaction of aa 301–538 or aa 914–1132 was detected (Fig. 4A and data not shown). The result seems to support a model that the homomeric interaction of hTERT occurs in a “head to tail” fashion. Our result cannot explain the previous result that the amino-terminal region (aa 1–300) and some truncated mutants (such as aa 301–1132) reconstituted telomerase activity (25). The region (aa 1–300) critical for telomerase activity (25, 26) may be not essential for the oligomerization but essential to interact with one or more critical factors such as hTR-binding proteins or Hsp90, which is recruited to telomerase by hTR or hTERT.

Functional oligomeric formations of telomerase have been proposed since two functional template RNAs in the telomerase complex having two active sites were found in S. cerevisiae and in humans (17, 18). In our experiments, the substituted mutant hTERT-D712A-V713I, bound to the wild-type hTERT in vivo and in vitro (data not shown) and inhibited its telomerase activity (Fig. 6), suggesting that oligomeric formation of the wild-type and the mutant hTERTs is the reason of the inhibition. The D712A or D712A-V713I mutants at the VDV sequence, which is critical for substrate binding, have been previously described as dominant negative mutants that eliminate endogenous telomerase activity and cause telomere shortening and cell senescence due to lack of telomerase activity (23, 31). However, the inhibitory effect of the mutant on the wild-type hTERT was not severe when transiently co-expressed in the telomerase-negative cells even if the amount of plasmid of the mutant was more than 10 times higher than the wild-hTERT (Fig. 6). The result seems to be consistent with the previous report by Beattie et al. (25) who observed a partial restoration of telomerase activity in the presence of hTERT-D712A and the truncated hTERTs harboring the intact pocket for active center but missing the amino-terminal region. These results suggest that the mutants defective in substrate binding (D712A or D712A-V713I) are not dominant negative enzymatically when these mutants oligomerized with the wild-type hTERT, although reconstituted telomerase activity of oligomers consisting of the wild-type and D712A or D712A-V713I hTERTs seems to be much weaker than that of the wild-type oligomer (Fig. 6) (25). The apparent dominant negative phenotype of D712A or D712A-V713I in the previous reports may be explained by a
huge difference in expression levels between endogenous hTERT and the ectopically expressed mutant hTERT, which may squelch out one or more critical factors for telomerase activity.

We expected that the truncated mutants, which have the hTERT-binding regions, would exhibit strong inhibitory effects on the wild-type hTERT by competing oligomerization of the wild-type hTERT. This strategy has been applied to HIV reverse transcriptase (14, 34). Telomerase maintenance is essential to the replicative potential of malignant cells, and inhibition of telomerase leads to telomere shortening and cessation of unrestrained proliferation (9, 10, 23, 31–33). The intrinsic property of hTERT to oligomerize may be an additional target to design specific inhibitors of telomerase. This strategy has been applied to HIV reverse transcriptase (14, 34–36).

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