Inactivation of the budding yeast telomere binding protein Cdc13 results in abnormal telomeres (exposed long G-strands) and activation of the DNA damage checkpoint. In the current study, we show that inactivation of Cdc13p induces apoptotic signals in yeast, as evidenced by caspase activation, increased reactive oxygen species production, and flipping of phosphatidylserine in the cytoplasmic membrane. These apoptotic signals were suppressed in a mitochondrial (ρ−) mutant. Moreover, mitochondrial proteins (e.g. MTCO3) were identified as multicopy suppressors of cdc13-1, suggesting the involvement of mitochondrial functions in telomere-initiated apoptotic signaling. These telomere-initiated apoptotic signals were also shown to depend on MEC1, but not TEL1, and were antagonized by MRE11, consistent with a model in which single-stranded G-tails in the cdc13-1 mutant trigger MEC1-dependent apoptotic signaling in yeast.

Cdc13p is a budding yeast telomere binding protein (1–3). Cdc13p appears to be a multifunctional protein involved in both telomere replication and protection (1–4). Its role in telomere replication has been suggested based on the findings that it interacts with the catalytic subunit of DNA polymerase α and an essential subunit of telomerase, Est1p (4). A mutation form of CDC13, cdc13-2, shows the telomerase negative phenotype (3). Its essential role in protecting yeast telomeres is presumably related to its binding to the exposed G-strand (1–3, 5). Cdc13p (P371S), a temperature-sensitive mutant form of Cdc13p, is unable to protect telomeres at the restrictive temperature (1). At the non-permissive temperature, cells with the cdc13-1 allele exhibit extensive degradation of telomeres from the 5′-ends, the C-rich strands (C-strands). The C-strand degradation results in long single-stranded G-tails (up to 20 kb) at the 3′-ends. The abnormal telomeres in cdc13-1 at the non-permissive temperature lead to RAD9-dependent cell cycle arrest at the G2/M phase, as well as cell death (1, 6). However, the mechanism of cell death triggered by Cdc13p inactivation is unclear. It was assumed that essential gene deletion because of the C-strand degradation is the cause of the cell death.

Yeast apoptosis is not well understood. Bax, Bcl-2, and other established apoptotic proteins have not been found in yeast cells. However, expression of human BAX in yeast induces cell death (7, 8), accompanied by mitochondrial alkalization and cytosol acidification (9). This process can be blocked by co-expression of human anti-apoptosis protein Bcl-2 (8). Additionally, aged mother cells and H2O2-treated cells have shown apoptosis markers in yeast, including flipping of phosphatidylserine (PS)1 from the inner leaflet to the outer leaflet of the cytoplasmic membrane, DNA damage (by TUNEL assay), and reactive oxygen species (ROS) induction (10, 11). More recently, a caspase-like protease Yca1p has been identified in yeast and was found to regulate yeast cell death induced by H2O2 treatment (12). Moreover, a broad range mammalian caspase inhibitor Z-VAD-fmk inhibits cell death in yeast induced by H2O2 treatment (12). In addition, like apoptosis in mammalian cells, yeast apoptosis is inhibited by the protein synthesis inhibitor cycloheximide (11).

In the current study, we show that inactivation of Cdc13p activates caspase activity, increases ROS production, and induces flipping of PS in the cytoplasmic membrane. Caspase activation and ROS induction were shown to be MEC1-dependent and antagonized by MRE11, suggesting the involvement of DNA damage signaling. Caspase activation appears to involve mitochondria and is linked to cell death because a mitochondrial mutant (ρ−) significantly suppressed caspase activation and cell death. Moreover, mitochondrial proteins have been identified as multicopy suppressors of cell death in cdc13-1.

Experimental Procedures

Yeast Strains—YPH cdc13-1a (MATa cdc13-1 his7 leu2-3 ura3-52 trp1-289), YPH cdc13-1a (MATa cdc13-1 his7 leu2-3 ura3-52 trp1-289) and the isogenic wild type (his7 leu2-3 ura3-52 trp1-289), W13a (MATa cdc13-1 his7 leu2-3, 112 ura3-52 trp1-289) and its isogenic wild type strain (MATa his7 leu2-3, 112 ura3-52 trp1-289), YPH499 tel1::HIS3, YPH499 mec1::URA3 slm1::TRP1 were obtained from the laboratory of Dr. Virginia A. Zakian (Princeton University, New Jersey). The haploid cdc13-1 mec1::URA3 slm1::TRP1 was generated by mating YPH499 mec1::URA3 slm1::TRP1 with W13a. The haploid cdc13-1 mec1::URA3 slm1::TRP1 was generated by mating YPH499 mec1::URA3 slm1::TRP1 with W13a. The haploid cdc13-1 mec1::URA3 slm1::TRP1 was generated by mating YPH499 mec1::URA3 slm1::TRP1 with W13a. The W13a ρ− strain was generated by growing W13a in a minimum medium containing 25 μg/ml ethidium bromide to saturation. The ethidium-treated culture was inoculated in the same medium containing the same ethidium and grew to saturation again, as described (13, 14). Under these conditions, essentially all clones will be ρ−. These ρ− clones are unable to grow in medium containing a non-fermentable carbon source (e.g. 2% glycerol).

PS Flipping—PS flipping was measured by using the ApoAlert annexin V-EGFP apoptosis kit from Clontech with modifications as in

1 The abbreviations used are: PS, phosphatidylserine; ROS, reactive oxygen species; FACS, fluorescence-activated cell sorter; FITC, fluorescein isothiocyanate; ss, single-stranded; ds, double-stranded; ATM, ataxia-telangiectasia mutated gene; ATR, ataxia-telangiectasia and Rad3-related; VAD-fmk, valyl-alanyl-aspartyl-[0-methyl]-fluoromethylketone.
Identification of Mitochondrial Proteins as Multicopy Suppressors of cdc13-1—In an attempt to isolate cdc13-1 suppressors, we transformed cdc13-1 with a yeast genomic library (15), which had inserts of about 1 kb in size linked to a Gal1 promoter. Two clones that suppressed the cdc13-1 temperature sensitivity at 34 °C were isolated. These clones were identified as fragments of YDR333C and antisense of CYC8 (Fig. 1). We also transformed cdc13-1 with a human HeLa cDNA library. Expression of cDNAs in this library is also under the control of the Gal1 promoter. One clone was isolated and identified as the mitochondrial protein MTCO3 (Fig. 1).

All three proteins, Ydr333Cp, Cyc8p, and MTCO3, are involved in mitochondrial functions. Ydr333Cp was found to interact with the mitochondrial ribosomal protein Mrp51p (16), which is involved in regulating the expression of COX2 and COX3 (17), subunits 2 and 3 of yeast mitochondrial cytochrome c oxidase, respectively. CYC8 encodes a protein that regulates expression of COX3 and COX6 of mitochondrial cytochrome c oxidase (18). MTCO3 is subunit 3 of human mitochondrial cytochrome c oxidase. As mitochondrial functions are known to affect apoptotic cell death in mammalian cells (14, 19), these results point to the possibility that cdc13-1 cells may die of apoptosis.

Inactivation of Cdc13p Triggers Apoptotic Signals in Yeast—To test whether cdc13-1 cells die of apoptosis, various known apoptosis markers were measured at the non-permissive temperature. A caspase inhibitory substrate conjugated with FITC (FITC-VAD-fmk) was used to monitor caspase activation in cdc13-1 cells (12). This compound can freely enter yeast cells and binds only to the activated caspase (12). The caspase activity can be measured by the intensity of the FITC fluorescent signal. As shown in Fig. 2B, after incubation of cdc13-1 at 37 °C overnight, about 60% of the cell population exhibited intense FITC fluorescence, indicative of caspase activation. Interestingly, 43.5% of cells survived the overnight incubation at 37 °C, which was monitored by plating the same samples at the permissive temperature (23 °C) (Fig. 2A). The caspase inhibitor, VAD-fmk, is a broad spectrum caspase inhibitor in mammalian cells. Yca1p, being the only identified caspase in yeast, is known to be inhibited by VAD-fmk (12). Consequently, caspase activation in cdc13-1 cells revealed by the use of FITC-conjugated-VAD-fmk is likely because of activation of Yca1p.

Another early event of apoptosis in mammalian cells is the increased production of ROS in mitochondria (14). Early log phase yeast cells, wild type and cdc13-1, incubates at room temperature or 37 °C were mixed with the compound dihydrorhodamine 123, which can be oxidized by ROS to become fluorescent chromophore rhodamine 123. Flow cytometric analysis of rhodamine 123 (Fig. 2C) showed an additional peak with more fluorescent intensity in cdc13-1 at 37 °C but not in the wild type strain at 37 °C. This result indicates that ROS was induced upon inactivation of Cdc13p.

We also checked the flipping of PS from the inner leaflet to the outer leaflet of the cytoplasmic membrane. PS is normally present in the inner leaflet of the bi-layer cell membrane in budding yeast (20), as in mammalian cells (21). During apoptosis, PS is transferred to the outer leaflet of the cell membrane in mammalian cells by an unknown mechanism, although the cell membrane structure is intact (21). PS has high affinity to a protein, annexin V (22, 23), and therefore can be detected by annexin V-EGFP. As shown in Fig. 2D, PS flipping, as revealed by surface fluorescence because of binding of annexin V-EGFP to the flipped PS in the outer leaflet of the membrane, occurred in cdc13-1 (bottom right panel) but not in the wild type strain (top right panel) at 37 °C. As shown in Fig. 2E, the annexin V-EGFP fluorescence signal revealed by FACS analysis was greatly enhanced upon inactivation of the telomere binding protein Cdc13p at 37 °C in cdc13-1 cells (bottom right panel) compared with that in cdc13-1 cells at room temperature (bottom left panel) or wild type cells at 37 °C (top right panel).

A Mitochondrial Mutant (ρ−) Rescues cdc13-1 and Suppresses cdc13-1-induced Caspase Activation—Mitochondria play a piv-

![Image]

**FIG. 1. Suppression of cdc13-1 temperature sensitivity.** A, suppression of cdc13-1 temperature sensitivity by overexpression of yeast and human cDNAs. W13a cells were transformed with a HeLa cDNA expression library or a yeast genomic library (all DNA inserts were under the control of the yeast Gal1 promoter for expression). Colonies at the non-permissive temperature (34 °C) were isolated and characterized. One human cDNA clone SC1 (MTCO3) and two yeast genomic DNA clones SC2 (YDR333C) and SC3 (antisense of CYC8) were identified. The plasmids carrying these cDNAs were purified and re-transformed into yeast cells. Wild type (wt) or cdc13-1 cells carrying indicated cDNAs were 10-fold serially diluted and spotted on plates. Plates were then incubated at 34 °C. All of these clones partially rescued the growth of cdc13-1 at the non-permissive temperature, 34 °C. B, identity of the suppressor clones. All cloned cDNAs were sequenced, and the identity of these clones was determined by gene bank data search. aa, amino acid residues.
otal role in apoptosis in mammalian cells (19). To test the involvement of mitochondria in cdc13-1 death, we generated a mitochondria-deficient mutant ρ0 in both wild type and cdc13-1 strain backgrounds using the ethidium method (13). Because these mitochondria-deficient cells cannot respire, they cannot utilize non-fermentable carbon sources such as glycerol. As

| Strains | survival (%) at 37°C |
|---------|---------------------|
| wt      | 87.9                |
| cdc13-1 | 43.5                |

Fig. 2. Inactivation of Cdc13p results in cell death and induction of apoptotic signals. A, loss of viability of cdc13-1 at the non-permissive temperature. Log phase wild type (wt) and cdc13-1 cells were incubated at 37 °C overnight. Cells were examined for both cell death (colony formation) and caspase activation (in B). For cell death measurement, cells were plated on YEPD plates at 23 °C. The number of colonies was counted. Cell survival (%) was expressed as the number of colonies divided by the number of colonies after overnight incubation at 23 °C. B, activation of caspase activity in cdc13-1. Wild type and cdc13-1 cells were incubated at either 23 °C (left panels) or 37 °C (right panels), followed by incubation with FITC-VAD-fmk, a FITC-conjugated inhibitory substrate of yeast caspase Yca1p. RT, room temperature. C, induction of ROS in cdc13-1 cells. Log phase wild type and cdc13-1 cells were incubated at either 23 °C (left panels) or 37 °C (right panels), followed by incubation with dihydrorhodamine 123 for 2 h. Rhodamine generated by ROS oxidation of dihydrorhodamine 123 was then analyzed by FACS. D, inactivation of Cdc13p induces PS flipping. Wild type and cdc13-1 cells were incubated at either 23 or 37 °C in YEPD medium. Log phase cells were digested by zymolyase and stained with annexin V-EGFP. Cells were then visualized by fluorescence (right panels) or regular light (left panel). E, FACS analysis of annexin V-EGFP fluorescence signals of wild type cells at 23 °C (top left) or 37 °C (top right) and cdc13-1 cells at 23 °C (bottom left) or 37 °C (bottom right).
shown in Fig. 3A (top four panels), ρ′ mutants grew in Glc but not Gly medium at 26 °C. ρ′ rescued cdc13-1 partially at a non-permissive temperature, 30 °C (Fig. 3A, bottom two panels). Suppression of cdc13-1 by ρ′ was observed up to 34 °C but not at 37 °C (data not shown).

To test if the ρ′ mutant blocks cdc13-1-induced caspase activation, we used the same caspase assay. As shown in Fig. 3B, the ρ′ mutant exhibited greatly reduced activation of caspase in cdc13-1 background (bottom panels).

MEC1 Plays an Important Role in Mediating Apoptotic Signals in cdc13-1 Cells—The essential protein Mec1, an ATM-like kinase (24), is a checkpoint protein and is involved in telomere maintenance (25–28). Its essential function can be separated from its checkpoint and telomere functions by deletion of Sml1p, which regulates the nucleotide pools (26, 28–30). To test whether Mec1p mediates apoptotic signals in cdc13-1 cells, we constructed the mec1Δ sml1Δ cdc13-1 mutant strain (also labeled as mec1Δ cdc13-1 in Fig. 4). The mutant mec1Δ sml1Δ cdc13-1 had a slight higher permissive temperature (about 29 °C), as previously reported (31). However, mec1Δ sml1Δ greatly reduced caspase activation (Fig. 4A) and ROS production (Fig. 4B) in cdc13-1. The reduction in apoptotic signals in the triple mutant is because of mec1Δ but not sml1Δ, because sml1Δ did not reduce the apoptotic signals (caspase activation and ROS induction) in cdc13-1 (data not shown). Both mec1Δ and mec1Δ sml1Δ mutants were viable and did not generate apoptotic signals (data not shown). Taken together, these results suggest that the MEC1 mediates the apoptotic signals generated by inactivation of Cdc13p.

We also tested the role of Tel1p in telomere-initiated apoptosis signaling. Like Mec1p, Tel1p is another yeast ATM homologue (24). Tel1p is known to be involved in telomere maintenance and checkpoint (32, 33). We analyzed multiple isolates of the tel1Δ cdc13-1 double mutant for caspase activation and ROS production. As shown in Fig. 4, C and D, unlike the mec1Δ cdc13-1 double mutant, the tel1Δ cdc13-1 double mutant showed slightly reduced caspase activation (C) and ROS production (D), suggesting that Tel1p is not significantly involved in telomere-initiated apoptotic signaling.

MRE11 Deletion Inhibits Apoptosis in cdc13-1 Cells—The MRE11/RAD50/XRS2 (MRX) complex has been shown to function in telomere length maintenance (32) and checkpoint activation by DNA double strand breaks (33). The MRX complex contains exonuclease activity and has been proposed to process double strand breaks for repair (33, 34). Deletion of any gene in the MRX complex abolishes the function of the complex and
therefore exhibits the same phenotypes (30, 32, 35). To study the roles of the MRX complex in cdc13-1-induced apoptosis, we constructed cdc13-1 mre11A double mutants.

The cdc13-1 mre11A double mutant had a lower maximum permissive temperature (26 °C) than the cdc13-1 single mutant (28 °C) (data not shown), in agreement with a previous report (36). The cdc13-1 mre11A double mutant died more extensively than the cdc13-1 single mutant after overnight incubation at 37 °C as assayed by plating at the permissive temperature (23 °C) (about 100-fold lower survival, data not shown). Similarly, the cdc13-1 mre11A double mutant exhibited more extensive caspase activation (Fig. 4E, right panel) and ROS induction (Fig. 4F, right panel) than the cdc13-1 single mutant. The mre11A single mutant was viable and did not activate caspase nor induce ROS (data not shown). These results suggest that the MRX complex may function in repairing damaged telomeres and thereby antagonizing telomere-initiated apoptotic signals.

**DISCUSSION**

**Inactivation of Cdc13p Triggers Apoptotic Signals in Yeast**—We have shown that inactivation of Cdc13p in cdc13-1 yeast cells leads to caspase activation, PS flipping, and increased ROS production (Fig. 2). These three events are major landmarks of apoptosis in mammalian cells (37) and have been demonstrated to occur in yeast (10–12). These apoptotic signals probably reflect cell death because caspase activation and cell death appear to be correlated (e.g. about 60% of cells were shown to undergo both caspase activation and cell death as shown in Fig. 2, A and B). Moreover, we demonstrated that a mitochondria-deficient p+ mutant suppressed both cdc13-1-induced caspase activation (Fig. 3B) and death of cdc13-1 cells at the non-permissive temperature (Fig. 3A).

The involvement of mitochondria in telomere-initiated apoptotic signals was also supported by suppression analysis. We have identified three multicopy suppressors of cdc13-1. Interestingly, these suppressors are either directly or indirectly related to mitochondrial cytochrome c oxidase. Inhibition of mitochondrial cytochrome c oxidase is known to trigger apoptosis in mammalian cells (38, 39). In addition, apoptosis has been shown to be associated with reduction of MTCO3 (40). Similarly, Bax-induced apoptosis in yeast has been shown to result in reduction of cytochrome c oxidase (8, 41). It seems possible that overexpression of cytochrome c oxidase may suppress apoptosis. Indeed, overexpression of subunit 3 of the human mitochondrial cytochrome c oxidase (MTCO3) resulted in reduced apoptotic signals in human 293T cells.2

We have noticed that none of the suppressors or the mitochondria-deficient strains can fully rescue cdc13-1 at 37 °C. In addition, cell death as measured by colony formation in mec1Δ sml1Δ cdc13-1 cells was almost the same as in cdc13-1 cells, although the apoptotic signals were essentially abolished in mec1Δ sml1Δ cdc13-1 cells (Fig. 4, A and B). However, the cell number in mec1Δ sml1Δ cdc13-1 did increase 3–5-fold compared with cdc13-1 after overnight incubation at 37 °C in agreement with a previous report (42). These results suggest that in addition to apoptosis, cdc13-1 cells may die through another cell death pathway(s). It is conceivable that essential gene deletion because of extensive degradation from the telomere end or mitotic catastrophe because of MEC1 DNA damage checkpoint defect may result in cell death by a pathway distinct from apoptosis in cdc13-1 cells.

**MEC1 Promotes Apoptosis in cdc13-1 Cells**—Both MEC1 and TEL1 are yeast homologues of the human ATM kinase (24) and are involved in telomere maintenance (25, 26, 30). Our studies have shown that MEC1 deletion can dramatically reduce (from 52 to 8%) caspase activation and ROS production in cdc13-1 cells (Fig. 4, A and B), suggesting that the apoptotic signaling in cdc13-1 cells is primarily mediated by MEC1. Surprisingly, TEL1 did not significantly affect caspase activation in cdc13-1 cells at the non-permissive temperature (Fig. 4, C and D).

Telomere dysfunction in human cells by inactivation of TRF2, a mammalian telomere binding protein (43), results in ATM-dependent apoptosis in some human cells (44). It has been suggested that MEC1 is more related to ATR whereas TEL1 is more related to ATM (45). It is unclear why telomere dysfunction in yeast triggers MEC1- rather than TEL1-dependent caspase activation. One possibility is that cdc13-1 inactivation and TRF2 inhibition produce different biochemical effects on telomeres. It is known that Cdc13p binds preferentially to single-stranded (ss) telomeric sequences (1), whereas TRF2 prefers to bind to double-stranded (ds) telomeric sequences at the ds/ss junctions and promotes t-loop formation (43, 46). Moreover, inactivation Cdc13p results in long ss G-tails, whereas inactivation of TRF2 results in loss of G-tails in apoptotic cells (44). Another possibility is that TEL1 plays a dual role at telomeres: damage repairing and checkpoint signaling, which would have opposing effects on caspase activation. Further studies are necessary to distinguish between these possibilities. In addition, it is worth noting that MEC1, but not TEL1, is involved in a telomere checkpoint pathway required for senescence in yeast (27).

**The MRX Complex Plays a Role in Protecting Telomeres**—Inactivation of Cdc13p has been shown to result in activation of the RAD9 checkpoint and arrest of cells in G2/M phase because of the generation of extended ss G-rich strands (1). It has been reported that the MRX complex acts upstream of RAD9 in activating checkpoint and DNA damage repair (33). The MRX complex also functions in telomere maintenance (32). Our results have shown that cdc13-1 mre11A double mutants died more extensively than the cdc13-1 single mutant and exhibited more extensive caspase activation and ROS production (Fig. 4, E and F), suggesting that the MRX complex antagonizes the telomere-initiated apoptotic signals. The simplest interpretation of this result is that the MRX complex may terminate the telomere-initiated apoptotic signaling by promoting homolo-

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2 T.-K. Li, H. Qi, and L. F. Liu, unpublished results.
uous recombination or non-homologous end joining at the de-
protected telomeres.

In the aggregate, our results suggest a model that is sche-
matically shown in Fig. 5. In this model, inactivation of
Cdc13-1p results in extensive degradation of the telomeric C-
matically shown in Fig. 5. In this model, inactivation of
gous recombination or non-homologous end joining at the de-
clear. It is conceivable, however, that the telomeres may play
extensive degradation of the telomeres may also
in apoptosis signals. The G-tails can also trigger
presumably through homologous and/or non-homologous re-
DNA damage in
is not clear if the initial signal is the exposed G-tails in mam-
death occurs in yeast upon exposure of the G-tails. Although it
nuclear mitochondrial apoptotic pathway leading to caspase activation and other apo-
death may play an important role in cell death regulation.
The G-tails can also trigger RAD9-dependent DNA damage signals under less severe conditions (1, 6). The DNA damage in cdc13-1 can be repaired by the MRX complex,
addition to apoptosis.

Our results suggest that apoptosis or apoptosis-like cell
dea occurs in yeast upon exposure of the G-tails. Although it
not clear if the initial signal is the exposed G-tails in mam-
requires homologous and/or non-homologous recom-
Telomere-initiated Apoptotic Signals in Yeast

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