Elongin C is a highly conserved, low molecular weight protein found in a variety of multiprotein complexes in human, rat, fly, worm, and yeast cells. Among the best characterized of these complexes is a mammalian E3 ligase that targets proteins for ubiquitination and subsequent degradation by the 26 S proteasome. Despite its crucial role as a component of such E3 ligases and other complexes, the specific function of Elongin C is unknown. In yeast, Elongin C is a non-essential gene and there is no obvious phenotype as associated with its absence. We previously reported that in Saccharomyces cerevisiae Elongin C (Elc1) interacts specifically and strongly with a class of proteins loosely defined as stress response proteins. In the present study, we examined the role of yeast Elc1 in the turnover of two of these binding partners, Snf4 and Pcl6. Deletion of Elc1 resulted in decreased steady-state levels of Snf4 and Pcl6 as indicated by Western blot analysis. Northern blot analysis of mRNA prepared from elc1 null and wild type strains revealed no difference in mRNA levels for Snf4 and Pcl6 establishing that the effects of Elc1 are not transcriptionally mediated. Reintroduction of either yeast or human Elongin C into Elc1 null strains abrogated this effect. Taken together, these data document that the levels of Snf4 and Pcl6 are dependent on the presence of Elc1 and that binding to Elc1 inhibits the degradation of these proteins. The results suggest a new function for yeast Elongin C that is distinct from a direct role in targeting proteins for ubiquitination and subsequent proteolysis.

Elongin C is a highly conserved, low molecular weight protein that is found in a variety of multiprotein complexes in human, rat, fly, worm, and yeast cells. Originally described as a component of the SIPI transcription elongation factor (1, 2), Elongin C and its orthologues have subsequently been identified as components of several multiprotein complexes, including the von-Hippel Lindau tumor suppressor complexes that ubiquitinate target proteins for subsequent proteolysis by the 26 S proteasome (3, 4).

Ubiquitination is an enzymatic cascade involving separate enzymes: E1, E2, and sometimes E3. In the first step, E1 forms a covalent intermediate with ubiquitin (referred to as ubiquitin activation), which is then transferred to E2. In combination with E3, the E2-bound ubiquitin is then transferred to the protein to be degraded (3, 5, 6). The proteins ultimately targeted by this cascade are often determined by the E3 ligase thus making it a key component of the complex (7).

von-Hippel Lindau disease is a hereditary cancer syndrome that frequently results in hemangiomas and renal cell carcinomas. The gene product, VHLp, acts as a classic tumor suppressor (2, 8–10). Recent evidence indicates that VHLp, in conjunction with Elongins B, C, Cul2, and Rbx1, forms a complex, referred to as VBC, which acts as an E3 ubiquitin-ligase (11–14). Among the targets of this activity is the HIF1-α transcription factor that is differentially regulated by interaction with VHLp under normoxic conditions (15, 16).

One of the earliest hints that VBC acts as an E3 ligase came from the resemblance of VBC to the yeast SCF complex (Skp1, Cdc53, F-box protein) that is a known E3 ligase (17–20). This is exemplified by the fact that the mammalian Elongin C shares homology with yeast Skp1 protein (21) and that Cul-2 is the homolog of Cdc53.

The region of homology shared between mammalian Elongin C and Skp1 is also highly conserved among the Elongin C genes from other species, including yeast. This suggests that yeast Elongin C (Elc1) might function in a similar manner to Skp1, that is, as part of an E3 ligase complex. Yet there is no evidence to support a role for Elc1 as a component of an E3 ligase in yeast. For example, our previous studies indicate that Elc1 does not interact with components of the SCF but instead interacts with a class of proteins that can be loosely defined as stress-responsive proteins (22). Among the strongest and specific Elc1 binding proteins are Snf4 and Pcl6. Snf4 is a positive regulator of the Snf1 kinase, which is responsible for the derepression of glucose-repressible genes (23–25). Pcl6 binds to Pho85 kinase and, based on sequence homology, is thought to be a Pho80-like cyclin. The Pho85 kinase is involved in a variety of cellular activities, including phosphate metabolism, glycogen metabolism, cell cycle regulation, and sugar metabolism (26–28). In this report, data are presented that demonstrate that Elc1 is involved in regulating the levels of two proteins thought to regulate these two protein kinases.

EXPERIMENTAL PROCEDURES

Yeast Strains, Media, and Methods—Saccharomyces cerevisiae strains used in this study are as listed. W303 (Yeast Stock Center) and its derivatives were used.

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Elc1 Stabilizes Interacting Proteins

W303α elc1Δ (22) strains were used for all yeast studies except presoma
degradation studies. Proteosomal degradation studies were car-
ried out with MHY 79α and MHY 80α (29), which were the generous
gift of Dr. Neil Mathias. Yeast cultures were grown in standard rich
YPD media or selective synthetic complete (SC) media containing 2%
(33). To induce expression of galactose-inducible plasmids, yeast cells
were grown in SC media containing 2% raffinose followed by
–

\[ \text{GPD1} \]

was used for the constitutive expression
–

\[ \text{TRP1} \]

markers, respectively, were used for the constitutive expression
of specific proteins under control of the
–

\[ \text{ADH1} \]

was examined from the slope of the linear regression lines.

To examine SNF4 gene expression, snf4 null and
elc1 null strains expressing pYeF1H-SNF4 were grown in to mid log
phase (\( 600 \) of 0.5–1.0) at 30 °C in CM-His with 2% galactose. RNA was
prepared using hot phenol glass beads method and separated by elec-
rophoresis on a 1.5-% formaldehyde gel as described (36). The SNF4
template used in the transcription reaction was

\[ \text{GPD1} \] and

\[ \text{TRP1} \]

were ligated into pBEVY-T under control of the
–

\[ \text{ADH1} \]

promoter. The plasmid pBEVY-T-HA-ELC1 was

\[ \text{HA} \]

produced by PCR amplification of HA-ELC1 from the plasmid

\[ \text{pYeF1H-ELC1} \]

with the oligonucleotides 178 (5’–GGGGCTACCGAGAA-

GCGAAAACTG-3’) and 464, which both add a

\[ \text{HA} \]

site. HA-ELC1 was then inserted directly into the

\[ \text{Kpn} \]

site of pBEVY-T, under control of the
–

\[ \text{ADH1} \]

promoter. pBEVY-T-Elongin C (mammalian)

\[ \text{HA} \]

was created by the digestion of the plasmid pSp72-Elongin C that was

\[ \text{Kpn} \]

the generous gift of Dr. William Kaelin. pSp72-Elongin C was digested

\[ \text{Bam} \]

with BamHI and BglII to isolate Elongin C. Elongin C was then direc-
tively inserted into the BamHI site in pBEVY-T, under control of the
–

\[ \text{GPD1} \]

promoter.

Western Blot Analysis—Yeast whole cell extracts were prepared as
described previously (22), and protein concentrations were determined by
Bradford assay (Bio-Rad, Hercules, CA). Protein extracts were then nor-
malized for loading as indicated and separated by electrophoresis and
electroblotted to nitrocellulose membranes as described previously (32).

To induce expression of galactose-inducible plasmids, yeast cells
were grown in selective SC media containing 2% glucose unless otherwise indicated (30–32). Transformation of plasmids
into yeast was achieved by standard methods as described previously

\[ \text{EcoRI} \] and

\[ \text{Bsu36I} \]

were digested with a rabbit polyclonal anti-Hrp1, which was the generous gift of Dr.

\[ \text{Mike Henry}. \]

Relative protein levels were determined by densitometry of
Western blots and normalized to a nonspecific cross-reaction protein that
is not affected by the Elc1status of the cells. Rates of degradation were
estimated from the slope of the linear regression lines.

RNA Analysis—To examine SNF4 gene expression, snf4 null and
elc1 null strains expressing pYeF1H-SNF4 were grown in to mid log
phase (\( 600 \) of 0.5–1.0) at 30 °C in CM-His with 2% galactose. RNA was
prepared using hot phenol glass beads method and separated by elec-
rophoresis on a 1.5-% formaldehyde gel as described (36). The SNF4
probe was generated by

\[ \text{in vitro} \]

transcription in the presence of

\[ \text{[α-}\text{32P]}\text{UTP} \]

. The SNF4 template used in the transcription reaction
was generated by PCR, which incorporated the T7 promoter into SNF4
using the primer set 461 (5’–TAATAGCTACATAGGAATGAGC-

TCTATGAGC-3’) and 449. The SNF4 antisense probe generated was

\[ \text{~664} \]

nucleotides. RNA transfer, hybridization, and procedures for
RNA analysis were followed as described previously (32, 37, 38).

PCL6 gene expression was examined in wild type and elc1 null
strains grown to mid-log phase (\( A_{600} \) of 0.5–1.0) at 30 °C in YPD with 2%
glucose. RNA was prepared and separated as described above. The
PCL6 probe was created by PCR, in the presence of

\[ \text{[α-}\text{32P]}\text{GTP} \]

, using oligonucleotides 390 (5’–CAAGCGGGCTGTTCTACAAAGGGAT-

GCGCGCGAGCTC-3’) and 391, following standard procedure (32). The PCR reaction
generated an antisense probe to PCL6 ~ 1500 nucleotides in length.
Transfer, hybridization, and analysis of RNA were accomplished as
done previously (32, 37, 38).

\[ \text{Dephosphorylation of Yeast Protein Extracts} \]

Protein extracts were made from wild type yeast cells expressing HA-tagged Pcl6. Total

\[ \text{Hrp1} \]

were used to analyze mRNA levels
–

\[ \text{PCL6} \] and

\[ \text{SNF4} \]

in wild type and elc1 null strains. Lane 1 contains
mRNA from W303-expressing HA-SNF4. Lane 2 contains mRNA from
W303Δelc1-expressing HA-SNF4. Lane 3 contains mRNA from W303-expressing
HA-PCL6. Lane 4 shows mRNA from W303Δelc1-expressing
HA-PCL6. Gels shown below the Northern blot correspond to the rRNA
from each strain and demonstrate equal loading.

Deletion of ELC1 results in decreased stability of Elc1
interacting proteins. A, total protein extracts were prepared from
both wild type and elc1 null strains expressing HA-tagged Pcl6 and
Snf4. Extracts were normalized for equal loading by Bradford analysis,
and 30 μg of each sample was examined. The Snf4 and Pcl6 were
visualized using mouse anti-HA antibody and horseradish peroxidase-
conjugated goat anti-mouse antibody with an ECL substrate. The levels
for the non-Elc1 interacting protein, Hrp1, were visualized using an
anti-Hrp1 antibody. B, levels of Pcl6 are reduced by ~70% in elc1 null
strains. Pcl6 levels were determined by scanning of Western blots from
three independent experiments. Normalization was to a nonspecific
cross-reacting protein whose levels do not change in elc1 null strains.

Deletion of ELC1 results in decreased stability of Elc1
interacting proteins.
protein extracts were then dialyzed against \( \gamma \)-phosphatase buffer (50 mM Tris-HCl, pH 7.5, 0.1 mM EDTA, 5 mM dithiothreitol, 0.01% Brij35, 10% glycerol) and incubated in the presence of \( \gamma \)-phosphatase (New England BioLabs, Beverly, MA) as described previously (39). HA-Pcl6 was then visualized by anti-HA Western blotting.

**RESULTS**

**Pcl6 and Snf4 Levels Are Decreased in Elc1 Null Strains**—Previous studies from this laboratory demonstrated strong and specific interactions of Elc1 with Pcl6 and Snf4 (22). These observations, coupled with the postulated role of mammalian Elongin C in protein complexes displaying E3 ligase activity, prompted us to examine the role of Elc1 in the turnover of Snf4 and Pcl6. To facilitate this analysis, SNF4 and PCL6 were separately cloned into pYeF1H, a plasmid that contains the hemagglutinin antigen (HA) epitope as an N-terminal tag, under the control of a galactose-inducible promoter (22, 34). Each of these plasmids was then transformed into both wild type and elc1 yeast cells, and the transformants were grown on the appropriate selective media. The elc1 null strain was constructed by insertion of the kanamycin resistance gene at the Elc1 locus and was confirmed by selection on kanamycin-containing plates, PCR amplification of the disrupted genomic region, and Northern blot analysis (22). After growth to mid-log phase and addition of galactose to induce PCL6 and SNF4 gene transcription, protein extracts were prepared and the levels of Snf4 and Pcl6 were determined by Western blotting. Fig. 1 shows representative data from these studies. First, the steady-state level of Pcl6 is markedly reduced in elc1 yeast cells compared with wild type cells (Fig. 1A). This is in contrast to a nonspecific cross-reacting protein whose levels do not change when comparing the two strains. Interestingly, Pcl6 appears as a doublet, and both species are equally reduced. To determine if this effect is specific to Pcl6, the levels of Snf4 were also examined in these strains. As shown in Fig. 1, the Snf4 levels are also markedly reduced in the absence of elc1. A third interacting protein, Yap4, was also examined and similar results were obtained (data not shown). The effect of elc1 on these proteins is specific, as demonstrated by the fact that the steady-state level of Hrp1, a protein that does not interact with Elc1, remains unchanged in the elc1 null strain (Fig. 1A).

**Pcl6 and Snf4 mRNA Levels Are Not Decreased in an Elc1 Null Strain**—Elongin C was originally described as a component of the transcription elongation factor SIII, or Elongin. Thus, the differences observed in the steady-state levels of Pcl6 and Snf4 in elc1 yeast cells compared with wild type cells (Fig. 1A) could be attributed to a role for Elc1 in transcriptional regulation. To address this possibility, SNF4 and PCL6 mRNA levels were compared by Northern blot analysis in wild type and elc1 null strains. As shown in Fig. 2, there is no difference in the PCL6 or SNF4 laboratories.
mRNA levels between wild type and elc1 null strains. These data suggest that the effects of Elc1 on Snf4 and Pcl6 are not due to decreased transcription elongation and subsequent decreases in RNA levels in the absence of Elongin C.

Because the presence of Elc1 does not affect the steady-state level of mRNA for Snf4 or Pcl6, one explanation for the observed reduction in the steady-state levels of these proteins is a role for Elc1 in mediating protein turnover. To explore this possibility, we examined the time course for degradation of Pcl6. Wild type and elc1 null strains expressing Pcl6 from a galactose-inducible promoter were grown to mid-log phase in selective SC media with 2% galactose. Subsequently, glucose (2%) and cycloheximide (50 μg/ml final concentration) were added to inhibit transcription and translation, respectively; aliquots were removed at short intervals from 0 to 60 min. Protein extracts were prepared from each aliquot, and the level of Pcl6 was determined by Western blotting. Fig. 3 shows that the level of Pcl6 is substantially reduced as early as 4 min after the transcription/translation shut-off in the elc1 null strain. In contrast, the level of Pcl6 remained constant in the wild type strain until 30 min after the shut off, at which point decreased levels of Pcl6 were observed. The cross-reacting band remained relatively constant throughout the time course, indicating that the effect is protein-specific. Semi-quantitative analysis of the Western blots by densitometry indicated that Pcl6 degradation in the elc1 strain was approximately twice as fast as in the wild type strain. Additionally, we did not observe a general reduction in proteins synthesis in the elc1 null versus wild type strain (as indicated by 35S labeling and examination of total protein composition by Coomassie Blue staining, data not shown). Although these results do not rule out the possibility that the reduction in steady-state levels of Pcl6 may be due to decreased translation initiation, they do confirm and extend the observation that the steady-state levels of Pcl6 are decreased in the absence of Elc1 (Fig. 1).

Elc1 Prevents Degradation of Pcl6 by the Proteasome—In mammalian cells, Elongin C is a component of an E3 ubiquitin ligase complex that targets protein substrates for degradation by the 26 S proteasome (10, 12, 13, 15, 16, 40). Yet the evidence presented above (Figs. 1–3) suggests Elc1 prevents degradation of its binding partners. This raises the possibility that Elc1 may prevent or inhibit targeting/degradation of proteins by the 26 S proteasome. To consider this possibility, we first determined if Pcl6 is indeed degraded in a proteasome-dependent manner. To this end, PCL6 was transformed into a wild type strain, MYH 803a and into MYH 792a, a strain that contains a temperature-sensitive mutant for the proteasomal subunit Doa3. Each strain was grown at the permissive temperature (23 °C) and the restrictive temperature (37 °C), and extracts were prepared for the measurement of Pcl6 levels by Western blot analysis. As shown in Fig. 4A, the levels of Pcl6 in the wild type strain remained constant regardless of growth conditions (compare lanes 3 and 4). However, in the doa3 strain, Pcl6 levels were markedly higher at the non-permissive temperature than at the permissive temperature (compare lanes 1 and 2) indicating that Pcl6 is degraded by the 26 S proteasome. Because protein phosphorylation has been observed to be a prerequisite for recognition by the E3 ligase and subsequent degradation by the proteasome (13, 41), it is notable that the different isoforms of Pcl6 are resolved on Western blots (as noted in Fig. 1). To determine if the different isoforms of Pcl6 are indeed due to phosphorylation, extracts were treated with λ-phosphatase and the resulting products were examined by Western blot. As shown in Fig. 4B, only one Pcl6 band is present after treatment with λ-phosphatase. Taken together, these results establish that Pcl6 is degraded by the 26 S proteasome and suggest the possibility that Elc1, by interacting with Pcl6, prevents its degradation.
Elc1 Stabilizes Interacting Proteins

**Reintroduction of Elc1 or Mammalian Elongin C into Elc1 Null Strains Restores the Steady-state Levels of Pcl6**—To confirm that the rate of Pcl6 degradation was dependent on the presence of Elc1, wild type and elc1 null strains were transformed with a plasmid that drives expression of Elc1. A strain transformed with a plasmid lacking an insert was also introduced, as a control. Following transformation, cells were grown to mid-log phase, protein extracts were prepared from each strain, and the level of Pcl6 was determined by Western blotting. As shown in Fig. 5A, reintroduction of Elc1 into the null strain results in restoration of Pcl6 levels to those of the wild type strain (compare lanes 3 and 4). The level of Hrp1, the non-interacting control, does not change among the four strains. Fig. 5B confirms that the expression of Elc1 correlates with those strains harboring the plasmid that contains the Elc1 insert.

Yeast and mammalian Elongin C are sufficiently conserved (41% identical, 71% similar) that the yeast protein is able to substitute for the mammalian protein in transcription elongation assays as well as in its binding to VHL (42, 43). Thus we examined the ability of mammalian Elongin C to substitute for yeast Elc1 in restoring Pcl6 levels in elc1 null strains. Human Elongin C was cloned into a high copy yeast vector and expressed in wild type and elc1 null strains as described above for yeast elc1. Total protein extracts were prepared, and Pcl6 levels were determined by Western blot analysis. The data shown in Fig. 5B demonstrate that introduction of mammalian Elongin C into elc1 null strains can completely substitute for the yeast protein and restore Pcl6 levels to that of the wild type strain.

**DISCUSSION**

Elongin C is a well-documented component of several multi-protein complexes, including the VHL tumor suppressor complex that ubiquitinates target proteins for subsequent proteolysis by the 26 S proteasome. Notably, Elongin C binding is essential for VHL tumor suppression activity, because mutations that interfere with their interaction result in loss of VHL tumor suppression and subsequent development of VHL disease (8, 9, 44). There is strong evidence to suggest the role of the VHL tumor suppressor complex as an E3 ubiquitin ligase that targets specific proteins such as HIF1-a and STRA13 for ubiquitin-mediated degradation (11–15, 40, 45). It has also been suggested that Glut1 levels may be regulated by the VHL complex, although it is not yet known if this is due to the E3 activity (46).

Although the evidence for a role of Elongin C in the VHL-directed E3 ligase is compelling, the data presented in this study suggests that in yeast, Elongin C influences protein stability in a manner that is distinct from its role as a part of the E3 ligase in mammalian cells. That is, Elongin C stabilizes interacting proteins and by extension does not participate in their targeting for proteolysis. In keeping with the notion of an alternative role for yeast Elongin C is the observation that mammalian Elongin C also exhibits additional functions, in particular roles that are similar to that postulated in yeast. For example, mutations in VHL that reside within the Elongin C binding site result in rapid degradation of VHLp, suggesting that the presence of Elongin C in the VHL complex is needed to stabilize the VHL protein (47). An additional study demonstrated that Elongin B/C binding to SOCS-1 (suppressor of cytokine signaling) prevents its degradation (44). Taken together, a model emerges suggesting that Elongin C may stabilize those proteins with which it interacts and in doing so may provide a structural framework that protects those proteins from degradation by the proteasome. In the present study we show that the levels of Snf4 and Pcl6 are affected by the presence of Elongin C. As both these proteins participate in the ability of the cell to utilize different carbon sources, the biological implication of the stabilization may be related to glucose utilization.

Evidence presented in this report demonstrates that binding to Elongin C prevents protein degradation. It is therefore curious that the related protein, Skp1, appears to play an apparent opposite role as an integral member of the SCF E3 ligase. In this light it is interesting that Mathias and co-workers (48) have presented a model for Skp1 functions within the E3 ligase as one that confers stability of the F-box protein, thereby regulating the abundance of Skp1 interacting proteins. This is the comparable role that we have uncovered for Elongin C and suggests that, although Elongin C and Skp1 interact with a distinct set of partners, they may indeed be performing the same function and that is to prevent degradation of target proteins. In the case of Skp1, the target for stabilization is the F-box proteins,cdc4 and Met30 (48, 49). In the work presented here, we show that the targets for stabilization by Elc1 are Pcl6 and Snf4. An extension of this model suggests that mammalian Elongin C has evolved to participate in targeting proteins that are comparable to the ones that interact with Skp1, i.e. factors participating in a E3 ligase complex. Hence, the similarity between Elc1 and Skp1 may define a new gene family whose role is to prevent degradation of their binding partners.

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**Binding to Elongin C Inhibits Degradation of Interacting Proteins in Yeast**
Linda E. Hyman, Edward Kwon, Sumana Ghosh, Jennifer McGee, Anna M. Boguszewska Chachulska, Tanya Jackson and William H. Baricos

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