Deletion of the RNA Polymerase Subunit RPB4 Acts as a Global, Not Stress-specific, Shut-off Switch for RNA Polymerase II Transcription at High Temperatures*

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We used whole genome expression analysis to investigate the changes in the mRNA profile in cells lacking the Saccharomyces cerevisiae RNA polymerase II subunit RPB4 (ΔRPB4). Our results indicated that an essentially complete shutdown of transcription occurs upon temperature shift of this conditionally lethal mutant; 98% of mRNA transcript levels decrease at least 2-fold, 96% at least 4-fold. This data was supported by in vivo experiments that revealed a rapid and greater than 5-fold decline in steady state poly(A) RNA levels after the temperature shift. Expression of several individual genes, measured by Northern analysis, was also consistent with the whole genome expression profile. Finally we demonstrated that the loss of RNA polymerase II activity causes secondary effects on RNA polymerase I, but not RNA polymerase III, transcription. The transcription phenotype of the ΔRPB4 mutant closely mirrors that of the temperature-sensitive rpb1-1 mutant frequently implemented as a tool to inactivate the RNA polymerase II in vivo. Therefore, the ΔRPB4 mutant can be used to easily design strains that enable the study of distinct post-transcriptional cellular processes in the absence of RNA polymerase II transcription.

RNA polymerase (RNAP) II is a highly conserved 12-subunit enzyme that is a component of a large protein complex involved in the regulated synthesis of eukaryotic mRNA (1, 2). Of the 12 yeast Saccharomyces cerevisiae RNAP II subunits, designated RPB1–RPB12, five have counterparts in bacterial RNAP. RPB1 and RPB2 are orthologs of the β′ and β subunits, respectively. RPB3 and RPB11 are structurally and functionally related to the bacterial α subunit pair (3, 4), and RPB6 is the ortholog of the α subunit (5).

In addition to the functional parallels that exist between bacterial and eukaryotic RNAP II subunits, there is extensive functional similarity between subunits comprising the three classes of RNAP. All but one of the RNAP II subunits, RPB4, have some functional relationship to a corresponding subunit in RNAP I and RNAP III. Five of the subunits are also identical in RNAP I, II, and III. Six other RNAP II subunits are related in sequence to subunits in either or both RNAP I and RNAP III. Therefore, the relatively small RPB4 subunit (221 amino acids, 25 kDa) has a function exclusive to RNAP II.

RPB4 interacts with RPB7, another small (171 amino acid, 19 kDa) essential subunit (6). This subunit pair can dissociate from the enzyme upon biochemical purification and deletion of the RPB4 gene from yeast cells results in diminished association of the RPB7 subunit with the enzyme. The purified RPB4-RPB7 subcomplex binds both single-stranded DNA and single-stranded RNA in vitro (7). A predicted oligosaccharide/oligonucleotide binding fold in RPB7 is crucial for both the nucleic acid binding and transcription activity of the subunit pair (7). However, the two functions are not absolutely linked since one RPB7 mutant causes a loss of transcription activity without affecting nucleic acid binding (7).

RPB4 and RPB7 are present at substoichiometric levels (~0.5 molecules per RNAP). Therefore, the most homogenous preparations of RNAP II are obtained from ΔRPB4 cells and used as a source of the enzyme for most general structural studies. Comparison of a lower resolution structure of the entire 12-subunit enzyme to the high resolution structure of the enzyme obtained from ΔRPB4 cells revealed differences in conformation; the wild type enzyme favors the closed conformation, and the mutant enzyme favors the open conformation (8, 9). RNAP II lacking the RPB4-RPB7 subcomplex forms a stable preinitiation complex with general transcription factors, and consequently, this subcomplex is required for a step following template commitment (7).

To learn more about RPB4 function, we determined how gene expression was altered in its absence. Using whole genome expression analysis coupled with additional in vivo experiments, we demonstrate that the loss of RPB4 results in a rapid and global decline in RNAP II-mediated transcription.

EXPERIMENTAL PROCEDURES

Total RNA Preparation and Northern Analysis—ΔRPB4 cells and a wild type counterpart that is genetically identical except at the mating type locus (WY4 (MATα) and N114 (MATα), respectively; Ref. 10) were grown in yeast peptone dextrose broth at 24 °C to an A₆₀₀ of 0.45–0.55 and then shifted to 37 °C by adding an equal volume of yeast peptone dextrose broth warmed to 50 °C. At specific times after the shift to 37 °C, cells were harvested by centrifugation at 20 °C and then frozen in a dry ice/ethanol bath and stored at −70 °C. Total RNA for microarray analysis was prepared by the glass bead method (11). Total RNA for Northern or slot blot analysis was prepared by the hot phenol procedure (12).

Ten micromgrams of total RNA were loaded into each lane of 1.2% agarose gels containing formaldehyde. RNA was transferred onto nitrocellulose membranes and cross-linked with ultraviolet light using a Stratalink (Stratagene). Immobilized RNA was hybridized with an
excess of 32P-labeled DNA probe at 42 °C in hybridization solution (5× SSPE (0.75 mM NaCl, 50 mM NaH2PO4, 5 mM EDTA, pH 7.4), 50% formamide, 1× Denhardt’s (0.2 mg/ml Ficoll 400, 0.2 mg/ml polyvinylpyrrolidone, 0.2 mg/ml bovine serum albumin), 0.1 mg/ml sheared salmon sperm DNA, 0.3% SDS) and then washed with a solution containing 2× SSPE and 0.2% SDS at 45 °C. The intensity of the remaining experiments were visualized on x-ray film and quantified by a PhosphorImager using ImageQuant (Molecular Dynamics). The gene fragments used as radioactive probes were as follows: ACT1, 1.4-kb HindIII/EcoRI; PGK1, 0.72-kb BamHI/EcoRI; PDA1, 0.97-kb NorI/HindIII; TUB1, 0.25-kb HindIII/rear1; RPL5, 0.7-kb EcoRI/HindIII; ACT1, 0.1-kb NosI/Styl; RPS14B, 1.0-kb NosI/Styl; RPL3, 0.75-kb BuII/XbaI; and RPL28, 1.2-kb SpeI/EcoRI.

**Quantification of RNA I and III Transcription Levels**—Ten micrograms of total RNA was hybridized with an excess of 32P end-labeled RNAP I or III-specific oligonucleotide probe at 55 °C for 12–16 h in 50 μl of hybridization solution (0.3 mM NaCl, 38 mM Hepes, pH 7.0, 1 mM EDTA, 0.1% Triton X-100). Mineral oil was overlaid to prevent evaporation of the hybridization mixture. Newly synthesized RNAP I and III transcripts were measured using oligonucleotides complementary to the junction of mature and processed RNA species, transcript probes for RNAP III (Fig. 5A and Ref. 13) and 25 S rRNA precursor for RNAP I (Fig. 4A). After hybridization, 450 μl of S1 nuclease digestion solution (0.3 mM NaCl, 60 mM NaOAc, pH 4.5, 2 mM ZnOAc, 0.02% Triton X-100, 150 μg/ml salmon sperm DNA, 0.3% SDS) was combined with the 50 μl of hybridization mixture and incubated at 30 °C for 30 min. The S1 nuclease digestion step was used to avoid differences in the expression of transcripts between samples and to allow for accurate measurement of RNApolymerase II. Because of the mating type difference, some of the transcripts showed 2-fold or more. Over half of these induced transcripts were not decreased by at least 2-fold, only 0.5% were decreased by 2-fold or more. Upon temperature shift, a drastic decline in mRNA abundance occurred. Expression of nearly all (98%) transcripts on the Affymetrix GenChip® Expression Analysis using GeneChip® Yeast Genome S96 Arrays. This array contains probes for over 6400 established S. cerevisiae open reading frames (ORFs), putative ORFs, and sequences of interest such as those encoding Ty element proteins, 2-μ plasmids, or mitochondrial proteins.

Grid format representation of the genome-wide expression profiles of ΔRPB4 mutant compared with wild type at the permissive temperature revealed a greater than 2-fold decrease in the expression of 26% of transcripts represented on the Affymetrix GeneChip® (Fig. 1, A and C). This decrease covers a variety of transcripts with no unifying features. However, upon temperature shift, a drastic decline in mRNA abundance occurred. Expression of nearly all (98%) transcripts on the Affymetrix GenChip® decreased by 2-fold or more, and 96% decreased by 4-fold or more (Fig. 1, B and D). These results suggest that RNAI in ΔRPB4 cells is essentially inactivated at 37 °C. Of the nominal percentage of transcripts whose level did not decrease by at least 2-fold, only ~0.5% were elevated by 2-fold or more. Over half of these induced transcripts were hypothetical open reading frames. The remaining handful of genes encoded mating type-specific genes (which are differentially expressed from the wild type strain of opposite mating type), a heat shock transcription factor, enzymes involved in glycolysis degradation, genes involved in DNA damage response, and a few other proteins involved in unrelated processes. These mRNAs may be vestiges of an early and rapid stress response (before the enzyme is fully inactivated) since ΔRPB4 cells are more sensitive to heat stress than wild type cells. However, because of the mating type difference, some of these apparently induced mRNAs may simply result from differential expression.

**mRNA Levels Drop Abruptly after Temperature Shift in ΔRPB4 Cells**—To examine how quickly the enzyme is inactivated at 37 °C, as well as confirm the whole genome expression data, we analyzed RNA samples from wild type and ΔRPB4 cells harvested 0, 15, 30, 45, 60, 120, and 240 min after temperature shift. Steady state mRNA levels were assessed upon hybridization of (dT)30 to equivalent amounts of immobilized total RNA samples (Fig. 2A). Our results show that ΔRPB4 cells have 46% lower levels of mRNA transcripts at permissive temperature relative to wild type. Upon temperature shift, there was a substantial (>5-fold), rapid, and sustained further decrease in steady state poly(A) RNA levels in mutant cells (a...
brief and minor drop in transcript levels due to the cellular stress response to heat shock is also noted in wild type cells; Fig. 2A). These results corroborate the array data and indicate that transcription by RNAP II is severely impaired 15 min after exposure of cells to 37 °C.

Gene-specific Effects Are Consistent with Genome-wide Expression Results—We also studied the effect of ΔRPB4 on transcription of a number of individual genes after temperature shift using conventional Northern analysis (Fig. 3). We analyzed four genes with relatively stable mRNA transcripts (half-lives greater than 25 min) at normal growth temperatures (30 °C), ACT1 (actin), PDA1 (pyruvate dehydrogenase a subunit), PGK1 (3-phosphoglycerate kinase), and TUB2 (tubulin; Fig. 3A). We also measured mRNA levels of five ribosomal protein genes, RPL3 (L3), RPL5 (L5), RPS14A (S14A), RPS14B (S14B), and RPL28 (L28; Fig. 3B). As documented previously, ribosomal protein transcript levels transiently drop in wild type cells after heat shock (Fig. 3B, WT 15 min lanes, and Ref. 15). In contrast, the ribosomal protein transcripts in ΔRPB4 did not display the same expression pattern (Fig. 3B, ΔRPB4 15 min lanes). Instead, transcript levels for all nine genes gradually diminished after the shift to 37 °C. Heat shock also resulted in a more prolonged, but transient, decrease in the levels of two of the four nonribosomal protein transcripts in wild type cells (Fig. 3A, PDA1 and TUB2). In contrast, in the ΔRPB4 mutant ACT1, PDA1, PGK1, and TUB2 mRNAs gradually decayed. The variability in mRNA decay rates of transcripts shown paralleled the published transcript half-lives (15). This phenomenon appears to result from transient repression, not from a temporary increase in ribosomal protein mRNA decay. Expression profiles of the five ribosomal protein transcripts from ΔRPB4 cells compared with wild type cells shifted to 37 °C revealed that this striking drop early after heat stress does not always occur in the mutant (Fig. 3C). Defective repression may account for the altered mutant profiles since transcription of genes required for the sudden, specific repression of ribosomal protein genes may already be hampered in mutant cells. After 30 min, when ribosomal protein transcript levels normally begin to rebound, the ΔRPB4 RNA polymerase is nearly fully inactivated, so transcript levels continue to spiral downward.

The expression data for the nine genes shown in Fig. 3 is consistent with our whole genome profiles since the levels of all transcripts decreased by 2-fold or more at the 45-min time point. In total, these results unequivocally demonstrate that the lethality of RPB4 at high temperatures is due to the shutdown of global gene expression.

RNAP II Loss of Function Also Affects RNAP I, but Not RNAP III, Transcription—The rapid loss of RNAP II activity has been shown to have secondary effects on transcription by other RNA polymerases (16) and on the abundance of ribosomal protein transcripts after temperature shift (15). To assess the ramifications of the loss of RNAP II activity on that of RNAP I and III, we measured the levels of newly synthesized tRNA (RNAP III) or rRNA (RNAP I) transcripts. tRNAs and rRNAs are extremely stable in comparison to mRNA transcripts (which have relatively short half-lives). Therefore, quantification of steady state levels of any given rRNA or tRNA is not an accurate barometer of changes in RNAP I or III activity.

RNAP I transcript levels were measured using a 35 S rRNA precursor oligonucleotide that was complementary to the junction of the rapidly processed spacer between the 5S and 25S rRNA transcript and 5' end of the 25S rRNA transcript (Fig. 4A). After annealing of the radioactively labeled oligonucleotide to RNA, the reactions were treated with S1 nuclease, and the products were separated by denaturing polyacrylamide gel electrophoresis. The activity of RNAP I goes down in the ΔRPB4 mutant, an effect also noted with two other mutants in either RPB1 or Srb4 that causes a rapid and comprehensive shutdown of RNAP II (Fig. 4B; Refs. 16 and 17). This effect is attributed to the yeast stringent response (18). This response is
triggered by amino acid deprivation (indirectly in this case due to the severe reduction in expression of amino acid genes and of genes encoding components of amino acid synthetic pathways) that leads to reduced synthesis of ribosomal proteins and rRNA. However, unlike the bacterial stringent response, tRNA and most mRNA synthesis is unaffected when yeast cells engage the standard stringent response upon direct amino acid deprivation.

For RNAP III, we used a tRNA oligonucleotide probe that is complementary to an intron-exon junction of a rapidly processed yeast tRNA (Fig. 5A). Our studies followed the synthesis of tryptophan tRNA in mutant and wild type cells (13). In this case, we found no decrease in the abundance of the newly synthesized tryptophan tRNA transcript (Fig. 5B, tRNAW). Therefore, the ΔRPB4 mutant directly acts on RNAP II causing a decrease in RNAP I, but not RNAP III, activity.

DISCUSSION

We have demonstrated that deletion of the S. cerevisiae RPB4 gene results in 1) enzyme inactivation at high temperature and 2) a decrease in transcription of a portion of genes at permissive temperature. This decrease in transcript levels is specifically associated with enzyme inactivation, not an increase in mRNA decay since the enzyme lacking RPB4 and RPB7 is severely deficient in gene-specific RNAP II activity in vitro (7, 19). This defect can be reversed in vitro by the addition of purified RNAP II (7, 19) or in vivo upon high copy expression of the RPB7 gene in ΔRPB4 cells (10). Structural studies of RNAP II purified from ΔRPB4 cells compared with the wild type enzyme also reveal that the portion of the enzyme that clamps DNA exists in a more open, less stable conformation (8, 9). Based on cumulative structural data (placing RPB4 and RPB7 downstream of the catalytic site in the center of the 25-Å cleft of the enzyme; Ref. 4) and biochemical data, Orlicky et al. (7) speculate that the RPB4-RPB7 subcomplex functions in stabilization of the promoter complex before initiation and/or stabilization of the early transcription complex before promoter escape. Therefore, the temperature-dependent alterations in enzyme activity documented here and published previously may result from the complete (at 37 °C) or partial (at 24 °C)
inability of RNAP II to form a stable association with the single-stranded DNA template or nascent RNA transcript.

Our whole genome expression profiles showed that at permissive temperature 26% of transcripts decreased by at least 2-fold relative to wild type (of these, 4% decreased by 4-fold or more). Therefore, the defects in \( \text{H9004} \) transcriptional activation seen at the permissive temperature recently reported by our laboratory and others (10, 20) likely extend beyond activation since a relatively large percentage of transcripts are affected. This 26% decrease does not closely correlate with the data we obtained for the permissive temperature time points of total RNA probed with (dT)\(_{30}\) (Fig. 2, \( \text{Oh} \)), where we measured a 46% overall decrease in steady state mRNA levels recovered from \( \text{H9004} \) cells before the temperature shift. This inconsistency is not surprising since each value was derived from different approaches. For example, expression of many genes may fall below normal levels but not reach the threshold 2-fold decrease required for inclusion in the whole genome expression data. Also, there may be inherent differences in mRNA levels at various phases of logarithmic phase growth.

Transcription alterations in \( \Delta \text{RPB4} \) cells parallel those documented for the \( \text{rpb1-1} \) mutant. This mutant contains a single G1437D amino acid change in conserved region H near the point where the carboxyl-terminal repeat domain of RPB1 emerges from the structure. \( \text{rpb1-1} \) displays a rapid and virtually complete shutdown of mRNA synthesis upon a temperature shift to 37°C (17, 21). \( \text{rpb1-1} \) is frequently used as either 1) a tool to study the ramifications of the absence of mRNA transcription on a variety of other cellular processes or 2) a tool to inhibit mRNA synthesis so that mRNA stability can be studied. Our data indicate that the effects of the RPB4 deletion mirror those of \( \text{rpb1-1} \); each causes a rapid inactivation of RNAP II activity at 37°C. In each mutant, this severe depletion of RNAP II activity results in a corresponding decrease in RNAP I activity but has no effect on RNAP III activity. Finally, as with \( \text{rpb1-1} \), we observed that ribosomal protein mRNA levels in the \( \Delta \text{RPB4} \) mutant do not drop rapidly and recover after exposure to 37°C but instead decay gradually (Fig. 3, \( B \) and \( C \), and Ref. 15).

The production of a stable deletion of the chromosomal copy...
of RPB4 is a simple, one-step procedure (22). In contrast, creation of a chromosomal point mutation is more time-consuming (22). Therefore, as proposed earlier (23), the ΔRPB4 mutant can be used in a straightforward method for creation of strains that enable heat inactivation of RNA II in vivo. Also, the ΔRPB4 mutant can be used to study the effects of other mutations in RPB1 on post-transcriptional events (e.g. the effect of carboxyl-terminal repeat domain mutants on mRNA processing events). However, since approximately one-quarter of all genes show a decrease in expression by 2-fold or more in ΔRPB4 cells, care must be taken to determine that the particular process of interest is not perturbed at permissive temperature in the deletion background. Whole genome expression data for rpb1-1 cells at permissive temperature (either 24 °C or the normal permissive temperature of 30 °C) is not currently available.

Of the hundreds of RNAP mutants studied to date, only two RNAP subunit mutants, a point mutation in RPB1 (rpb1-1) and now the ΔRPB4 mutant, are known to rapidly inactivate the enzyme at high temperatures. Select mutants in RNAP II holoenzyme components (Med2, Med6, Srb10, Srb4, and Srb5) have been subjected to whole genome expression analyses (17, 24). Only the srb4-138 mutant causes a rapid and extensive decrease in transcript levels analogous to rpb1-1 (16, 17). In the srb4-138 point mutant, 93% of the 5361 genes scored (the number of genes whose expression decreased by 2-fold or more in rpb1-1) were down 2-fold or more (17). Although the decrease in gene expression in the srb4-138 mutant is broad, it is not quite as comprehensive as the 98% decrease seen with the ΔRPB4 mutant.

For many years, studies have focused almost exclusively on the defective heat stress responses noted in the absence of RPB4 (25–28). However, our data demonstrates that this defect represents only a portion of the total picture. Maillet et al. (23) also found inconsistencies in the previously proposed links between ΔRPB4 cells and the stress response deficiencies. Two-dimensional gel electrophoresis of wild type versus ΔRPB4 proteins revealed a lack of induction of more than 50 heat shock proteins in the mutant at 38 °C, while other stresses were unaffected (23). The protein expression patterns in ΔRPB4 and rpb1-1 mutants were similar under 38 °C heat shock conditions, and the levels of three RNAP II transcripts, DED1, ACT1, and STE2, decreased in the ΔRPB4 mutant (23). Consequently, Maillet et al. (23) suggested that both rpb1-1 and ΔRPB4 cells have a general effect on transcription at the non-permissive temperature. Another laboratory had also found minimal effects on transcriptional activation upon cell wall stress or exposure to high salt (29). Our results support the earlier studies and conclusively demonstrate that the transcriptional ramifications of the ΔRPB4 subunit are analogous to those of rpb1-1. The effects of the deletion of the RPB4 are global and are not limited to heat shock or other stress proteins. Therefore, this mutant can be used as an alternate, easier tool for creation of a heat-inactivatable RNA II enzyme.

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