Transcription by RNA polymerase II induces changes of DNA topology in yeast

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We show that induction of transcription of a CYC1–lacZ fusion gene, borne on a yeast plasmid, causes an increase in negative superhelicity of approximately five turns. This increase is abolished by deletion of either essential element of the CYC1 promoter, the upstream activation site (UAS), or the TATA boxes. Several experiments indicate that the size of the increase is proportional to the size of the transcribed region. First, an internal deletion removing half of the CYC1–lacZ transcribed region results in a plasmid whose negative superhelicity on induction is intermediate between promoter-deletion plasmids and the parental plasmid. Second, plasmids bearing insertions of a fragment containing the putative CYC1 terminator into the CYC1–lacZ fusion gene have relative negative superhelicities proportional to the length of the truncated fusion transcripts generated. A plausible model explaining these observations is that local unwinding of the double helix by transcribing RNA polymerase generates positively supercoiled DNA, which is subsequently relaxed by a topoisomerase.

[Key Words: RNA polymerase II transcription; negative supercoiling; transcription termination]

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DNA isolated from many different organisms has been found to be underwound or negatively supercoiled. In Escherichia coli, the extent of negative supercoiling is controlled by the opposing activities of the type I topoisomerases and DNA gyrase. Although gyrase introduces negative supercoils, the type I topoisomerases tend to relax negative supercoils [Wang 1985]. Another possible source of negative superhelicity is suggested by experiments in vitro. Wang et al. [1977] showed that negative supercoils were introduced into a nicked plasmid by the unwinding of the double helix by RNA polymerase in the presence of DNA ligase. In the same manner, the combined action of in vitro transcription by RNA polymerase and topoisomerase introduced negative supercoils into a closed, circular DNA. The transcription of DNA by RNA polymerase unwound the helix, introducing positive supercoils. Relaxation of the positively supercoiled DNA by topoisomerase resulted in a net decrease in linking number, i.e., an increase in negative superhelicity [Gamper and Hearst 1982].

In eukaryotes, the mechanism by which negatively supercoiled DNA is generated is less clear. In principle, the negative supercoiling found in deproteinized, episomal DNA could be attributed to the wrapping of DNA into nucleosomes in vivo. Topoisomerases have been identified in all eukaryotes examined, ranging from yeast to mammals. However, although these enzymes will relax supercoiled DNA, they will not introduce negative supercoils like E. coli DNA gyrase. In yeast, two genes, TOP1 and TOP2, have been shown to encode topoisomerases [Goto and Wang 1984, 1985; Thrash et al. 1985; Uemura and Yanagida 1986], and these enzymes have been implicated in several critical cellular events. The product of the TOP2 gene was first shown to be required to decatenate newly replicated 2μ DNA [DiNardo et al. 1984]. Because the TOP2 gene product was shown to act in the M phase of the cell cycle and top2 mutant cells could not segregate their chromosomes properly, it was inferred that the enzyme is also required for decatenation of newly replicated yeast chromosomes [Holm et al. 1985; Uemura and Yanagida 1986].

Although eukaryotic topoisomerases have been implicated directly in replication, their role in transcription is less certain. Experiments in Drosophila have demonstrated a physical association of topoisomerase I with transcribed DNA [for review, see Wang 1985]. In Saccharomyces, the presence of either the TOP1 or TOP2 products was shown to be needed for transcription of the rDNA repeats by RNA polymerase I but not for transcription of the GAL1 gene [Brill et al. 1987]. Thus, these experiments do not link a topoisomerase to RNA polymerase II transcription. It is possible that the block to rDNA transcription operates at the level of initiation at the rDNA promoter. In E. coli, topoisomerase mutations have been shown to alter the activities of numerous promoters [for review, see Gellert 1981; Stenglanz et al. 1981]. It is also possible, as proposed, that topoisomerases act as swivels to relieve positive torsional stress generated by transcription within the rDNA cluster [Brill et al. 1987]. Such stress would be due to unwinding of the DNA by the transcriptional machinery.

In this paper, we show a link between topoisomerase action and transcription by RNA polymerase II. We demonstrate that induction of transcription of a CYC1–lacZ gene results in an increase of negative supercoiling of a plasmid in Saccharomyces cerevisiae. This increase
is abolished by deleting the CYC1 UAS or TATA boxes and is intermediate in plasmids containing shortened transcripts. One means by which shortened transcripts are generated is by insertion of the CYC1 terminator into the CYC1–lacZ gene. Our results are discussed in terms of a model proposing that unwinding of the template by transcribing RNA polymerase creates torsional stress that is adjusted by the action of a topoisomerase.

**Results**

*A system to detect transcriptionally induced changes in supercoiling*

We sought to devise a system to maximize the chance of detecting changes in supercoiling induced by transcription. A simple method to separate topoisomers of a plasmid is gel electrophoresis in the presence of an intercalator, such as chloroquine. By this means, a supercoiled plasmid will be displayed as a distribution of topoisomers that differ, one from the next, by one superhelical turn (or a difference of one in linking number). The most intense band at the center of a distribution denotes the average superhelical density. The plasmid LG-312 (Guarente and Mason 1983) has several features that make it suitable for a study of transcriptionally induced changes of supercoiling in yeast (Fig. 3a). First, the plasmid contains a highly regulated promoter, that of the CYC1 gene of yeast. Second, induction is expected to result in a substantial increase in the number of RNA polymerases transcribing from the plasmid. This increase is expected because the induced CYC1 promoter is fairly strong and because the transcript initiated at this promoter is relatively long, covering 7 kb of the plasmid before ending at the distal end of the Amp [β-lactamase] gene. The remaining 4 kb of the plasmid is taken up by the URA3 gene and an untranscribed segment bearing the 2μ origin of replication [Broach 1981]. We reasoned that the increase in the number of RNA polymerase molecules on the plasmid after induction could result in a detectable increase in negative supercoiling, as observed for *E. coli* RNA polymerase in vitro [Wang et al. 1977; Gamper and Hearst 1982].

**Analysis of supercoiling in repressing and inducing conditions**

Cells bearing pLG-312 were grown in conditions in which the CYC1 promoter is repressed (in glucose medium), or fully induced (in lactate medium). DNA was isolated from cells, phenol extracted, electrophoresed in the presence of two different concentrations of chloroquine, and transferred to nylon. The topoisomers were revealed by hybridization to an internal *lacZ* fragment. As shown in Figure 1, the topoisomers from the induced cells migrated faster than the topoisomers from the repressed cells. Because an increase in the concentration of chloroquine, which decreases negative supercoiling, slowed the migration of topoisomers (Fig. 1b), it follows that the faster migrating topoisomers are more negatively supercoiled.

This result alone does not rule out the possibility that the difference in the linking number of pLG-312 is an indirect consequence of growth in glucose or lactate media and is not related to transcription of the CYC1–lacZ gene. That this is not the case is suggested by the observation that the endogenous 2μ plasmid, or pLG-312 derivatives that are deleted for essential CYC1 promoter...
promoter elements (Guarente and Mason 1983), have the same superhelical density in glucose and lactate media (data not shown).

Effects of promoter deletions on supercoiling

If the increase in negative supercoiling of pLG-312 were a direct consequence of transcription, deletion of essential elements of the CYC1 promoter should prevent the increase. In Figure 2, we show that deletion of either the CYC1 UAS or the TATA region, both of which are essential for transcription of the gene (Guarente and Mason 1983), abolished the increase in negative superhelicity in inducing conditions. A densitometric scan of this autoradiogram indicates that the difference in linking number due to the CYC1 UAS is about five turns.

Effects of alterations in the size of the transcribed region on supercoiling

We wished to investigate whether altering the size of the CYC1–lacZ transcriptional unit would exert a corresponding effect on the change in supercoiling. We describe two approaches that shorten the transcriptional unit, internal deletion and employment of the putative CYC1 terminator. In the first approach, an internal fragment of 4 kb was deleted from the 7-kb transcriptional unit. To recreate a plasmid of the same size and sequence as pLG-312, this fragment was inserted into an untranscribed region on the plasmid (Fig, 3a; Broach 1981). As shown in Figure 2, the rearranged plasmid pBT + B has a superhelical density upon induction that is intermediate between pLG-312 and the derivatives bearing promoter deletions.

In the second approach, we employed an 83-bp DNA fragment that includes sequences necessary for 3'-end formation of the convergently transcribed CYC1 and UTR1 genes (Fig. 3b; Zaret and Sherman 1982). It was first necessary to demonstrate that this small fragment was capable of specifying 3'-end formation. Accordingly, the fragment was cloned into three different sites in the CYC1–lacZ gene, 0.1 [BamHI], 2.0 [Sacl], and 4.0 [TthI111] kb from the promoter (see Fig. 3a). The Northern gel in Figure 4 shows that in either orientation at the Sac1 or TthI111 sites, the inserted fragment generated truncated transcripts of the expected sizes and prevented any read-through transcription. However, at the BamHI site, the fragment was functional in only one orientation, the CYC1 [C] orientation. We think that our inability to detect the truncated transcript in this case was due to its small size, ~150 bases, but we cannot rule out the remote possibility that the fragment destabilizes a transcript that reads-through with detectable efficiency. In the UTR1 [U] orientation, full-length CYC1–lacZ message was seen at normal levels. We do not know why the fragment allowed read through in this particular construction. It is possible that the sequence TATAAA, present on the coding strand twice in this ori-

Figure 2. Southern analysis of DNA from cells transformed with plasmids bearing intact, promoter-deleted, and internally deleted CYC1–lacZ fusion genes. DNA was prepared from BWG1-7a transformants grown in inducing conditions, electrophoresed in a chloroquine gel, and blotted as described in Materials and methods. (a) DNA from cells transformed with pLG-312, which bears an intact CYC1–lacZ fusion gene. (b) DNA from cells transformed with pBal6, which deletes the TATA boxes from the CYC1–lacZ fusion gene. (c) DNA from cells transformed with pLG-178, which deletes both UAS1 and UAS2 from the CYC1–lacZ fusion gene. (d) DNA from cells transformed with pBT + B, which deletes 4 kb from the 7-kb CYC1–lacZ–transcribed region (see Fig. 3). (e) Densitometric tracings of topoisomers shown in a–d.
Transcription and DNA topology

Discussion

In this paper we have shown that induction of a CYC1-lacZ fusion caused an increase of approximately five negative superhelical turns in the plasmid bearing the gene. This increase depended on transcription because it was abolished in plasmids deleted for essential promoter elements, either the CYC1 UAS or TATA region. Furthermore, the size of the increase in negative superhelicity was proportional to the length of the CYC1-lacZ transcript: An internal deletion of 4 kb of the 7-kb transcriptional unit resulted in a reduced change in DNA superhelicity. Insertion of a putative yeast terminator into the transcribed sequences resulted in a relative superhelical shift that increased with the distance from the site of insertion to the promoter.

Figure 3. Diagram of the parental plasmid pLG-312, the plasmid BT+B with an internally deleted CYC1-lacZ fusion gene, and plasmids BI02OC, BI02OU, BI03OC, BI03OU, BI04OC, and BI04OU, which bear insertions of a putative terminator from the 3' end of CYC1 into the CYC1-lacZ fusion gene. (a) Plasmid LG-312 bears the parental CYC1-lacZ fusion gene. In pBT+B, the 4-kb BamHI-Tthl1111 fragment is taken out of the 7-kb CYC1-lacZ transcribed region, leaving the promoter intact, and inserted back into the untranscribed 2kb region of the plasmid at XbaI. Plasmids BI03OC, BI03OU, BI02OC, BI02OU, BI04OC, and BI04OU are insertions of the 83-bp AvaII–FnuDII CYC1 fragment into the BamHI, SacI, or Tthl1111 sites of pLG-312. The letters C (CYC1) and U (UTR1) denote the two possible orientations of the fragment, as in b. (b) The putative terminator is an 83-bp AvaII–FnuDII fragment lying between the convergently transcribed CYC1 and UTR1 genes. Sequences on this fragment are necessary for 3'-end formation of the CYC1 and UTR1 mRNAs (Zaret and Sherman 1982).

Figure 4. Northern analysis of RNA from cells transformed with plasmids bearing insertions of a putative terminator into the CYC1-lacZ fusion gene. RNA was isolated from BWGl-7a transformants grown in inducing conditions, electrophoresed, and blotted as described in Materials and methods. (a) RNA from cells transformed with pLG-312, the parental plasmid, which produces CYC1-lacZ mRNAs with an average length of 7 kb. (b) RNA from cells transformed with BI03OC, where the putative terminator is inserted 100 bp from the CYC1 promoter (BamHI) in the CYC1 orientation. (c) RNA from cells transformed with BI02OC, where the putative terminator is inserted 2.0 kb from the CYC1 promoter (SacI) in the CYC1 orientation. (d) RNA from cells transformed with BI04OC, where the putative terminator is inserted 4.0 kb from the CYC1 promoter (Tthl1111) in the CYC1 orientation. (e) RNA from cells transformed with BI03OU, where the putative terminator is inserted 100 bp from the CYC1 promoter (BamHI) in the UTR1 orientation. (f) RNA from cells transformed with BI02OU, where the putative terminator is inserted 2.0 kb from the CYC1 promoter (SacI) in the UTR1 orientation. (g) RNA from cells transformed with BI04OU, where the putative terminator is inserted 4.0 kb from the CYC1 promoter (Tthl1111) in the UTR1 orientation.
Although our results provide a link between transcription and superhelical density, indirect changes in supercoiling could result. It is unlikely that the observed changes in superhelicity result from a disruption of nucleosomes, however, because such an alteration would increase supercoiling in the positive direction.

A clue as to mechanism may be provided by the relationship between the size of the transcribed region and the magnitude of the increase in negative supercoils. We suggest that the transcriptionally induced increase in negative superhelicity results from an increase in the number of RNA polymerase molecules within a transcription unit. On induction, the local unwinding of the double helix by transcribing RNA polymerases would produce a positive torsional stress that could be removed by a topoisomerase activity. Because the yeast RNA polymerase II unwinds 14 bp in vitro (Pedone and Ballario 1984), a decrease in the linking number of five predicts the presence of three to four RNA polymerase molecules transcribing the induced CYC1–lacZ fusion at any given moment. This figure is in line with a rough estimate of the frequency of initiation at the CYC1 promoter, based on estimates of the number of transcripts per cell and the half-life of the message (Zitomer et al. 1979).

A picture slightly more complicated than the above has emerged from studies on an E. coli plasmid, with or without a functional promoter for the tet gene (Pruss and Drlica 1986). In this case, a transcriptionally induced increase in negative supercoiling was observed only in a strain missing the type I topoisomerase encoded by topA. It has been suggested that the transcribing RNA polymerase generates positive stress ahead of itself and negative stress behind itself, both of which are relaxed by the action of topoisomerases (Liu and Wang 1987). Because the topA product relaxes negative but not positive supercoils, an accumulation of negative supercoils would be in evidence in a topA mutant. Because yeast type I topoisomerases do not show a preference for relaxing positive or negative supercoils, we do not favor this model to explain our results. In addition, the yeast strain employed in our studies has type I topoisomerase activity (B.I. Osborne and L. Guarente, unpubl.).

Previous experiments in yeast showed that transcriptional activation of the silent mating-type loci resulted in a decrease in negative supercoiling (Abraham et al. 1983). We believe that the difference between these results and ours may relate to the specific mechanism operating to repress the silent mating-type genes. This mechanism has been associated with an origin of replication and with substantial changes in chromatin structure at the silent loci (Brand et al. 1987). These additional factors may cloud a change in supercoiling that was specifically associated with transcription.

The role of topoisomerases in transcription

Previous studies show that transcription by yeast RNA polymerase II can continue in the absence of the TOP1 and TOP2 gene products (Brill et al. 1987). In these experiments, induction of chromosomal GAL genes was monitored after shift of a top1 top2Δ strain to the non-permissive temperature. One might have concluded from our results that the continued action of topoisomerases would be required for RNA polymerase action. A major difference between our system and the GAL loci studied is that the CYC1–lacZ transcriptional unit re-
DNA isolation and Southern blotting

with 2-propanol. Precipitates were resuspended in TE and ex- 

ously and immediately placed in boiling water for 3 min. Tubes

mg/ml solution of zymolyase 100-T (Seikagaku Kogyo) was

ml plastic microfuge tubes. Twenty five microliters of a 3

tracted twice with phenol-chloroform-isoamyl alcohol

(25 : 25 : 1). One-half the final precipitate was used per gel lane.

Implications for yeast mRNA 3’-end formation

In higher cells, the formation of mRNA 3’ ends is dic- 
tated in part by the AAUAAA RNA cleavage signal and by 
termination sequences that lie downstream of the 
signal, as shown by nuclear run-on assays (for review, 
see Frayne et al. 1984; Wickens and Stephenson 1984; 
Birnstiel et al. 1985; Falck-Pedersen et al. 1985; Hart et 
al. 1985). Our results show that the 83-bp fragment at 
the 3’ end of CYCI, taken from a region required for the 
formation of the 3’ end of the CYCI mRNA (Zaret and 
Sherman 1982), is capable of 3’-end specification when 
inserted into the body of a transcribed region. Further­ 
more, the finding that the fragment-bearing constructs, 
like the internally deleted construct, exhibited a reduc­ 
tion in negative supercoiling compared with pLG-312 
and RNA preparation were performed as described previously 
and RNA preparation were performed as described previously

by the random primer method (Feinberg and Vogelstein 1984).

At least four blots were performed per figure, using DNA 
from independent transformants, with visually indistinguish­ 
able results. Band intensity was assessed by laser densitometry.

Materials and methods

DNA isolation and Southern blotting

DNA isolation and Southern blotting

Gels were run in Tris-phosphate, according to Shure et al. 
(1977), in 0.5% agarose with 4 (Fig. 1 only) or 2 µg/ml chloro­ 
quione (Sigma). Gel transfer to GeneScreen Plus (New England 
Nuclear), hybridizations, and washes were done according to 
the method of K.C. Reed (Bulletin 1234, BioRad Laboratories, 
Richmond, CA) and Reed and Mann (1985). Northern blotting 
and RNA preparation were performed as described previously

yeast strains, transformation, and media

Plasmids

Plasmids LG-669Z, LG-312 (Guarente and Mason 1983), LG-178 
(Guarente et al. 1984), and Bal6 (Hahn et al. 1985) have been 
described. Plasmid BT + B was derived from pLG-312, first by 
cutting with BamHI and Tth111, filling in, and inactivating, 
the pBT. The BamHI-Tth111 fragment of pLG-312 was purified 
along with Xbal-cut pBT. The DNAs were filled in with 
Klenow fragment (Boehringer) and ligated together, so that 
the Tth111 site was nearest URA3, making pBT + B. The 
plasmids B102OC, B102OU, BI03OC, BI03OU, BI04OC, 
and BI04OU were derived from pLG-669Z, the parent of 
plg-312. The Sma1-Sma1 fragment of pLG-669Z was deleted, 
generating pASma. A Sall 8-mer (New England Biolabs) was li­ 
gated into pASma cut with BamHI, SacI, or Tth111 filled in, 
making BI03O, B1O2O, and B104O, respectively. Addition of the 
Sall 8-mer at these sites has no effect on transcriptional read 
through or superhelical density when compared to pLG-312 
data not shown). The 3’ end of CYCI was subcloned as follows: The 83-bp 
AvalI–FnuDII fragment was purified from a digest of pCYCI 
[Smith et al. 1979], filled in, and ligated into filled-in Sall, 
Aval-cut pBR322. This ligation restores Aval and Sall in the 
proper orientation. This intermediate plasmid was cut with 
Aval, filled-in, and a Xhol 8-mer (New England Biolabs) was 
added, making BI02O, from which the Aval–FnuDII fragment 
can be excised by Xhol, Sall digestion. The Xhol–Sall fragment 
was ligated into Sall-cut B102O, B103O, and B104O in the 
CYCI (C) and UTRI (U) orientations, making B102OC, B102OU, 
B103OC, B103OU, B104OC, and B104OU.

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