Topological Effects of the TATA Box Binding Protein on Minicircle DNA and a Possible Thermodynamic Linkage to Chromatin Remodeling[†]

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ABSTRACT: DNA ring closure experiments on short restriction fragments (∼160 bp) bound by the TATA box binding protein (TBP) have demonstrated the formation of negative topoisomers, consistent with crystallographically observed TBP-induced DNA untwisting but in contrast to most previous results on topological effects in plasmid DNA. The difference may be due to the high free energy cost of substantial writhe in minicircles. A speculative mechanism for the loss of TBP-induced writhe suggests that TBP is capable of inducing ΔTw between 0 and −0.3 in minicircles, via loss of out-of-plane bending upon retraction of intercalating Phe stirrups, and that TBP can thus act as a "supercoil shock absorber". The proposed biological relevance of these observations is that they may model the behavior of DNA in constrained chromatin environments. Irrespective of the detailed mechanism of TBP-induced supercoiling, its existence suggests that chromatin remodeling and enhanced TBP binding are thermodynamically linked. Remodeling ATPases or histone acetylases release some of the negative supercoiling previously restrained by the nucleosome. When TBP takes up the supercoiling, its binding should be enhanced transiently until the unrestrained supercoiling is removed by diffusion or topoisomerases. The effect is predicted to be independent of local remodeling-induced changes in TATA box accessibility.

Eukaryotes use combinations of transcription factors to regulate transcription initiation by RNA polymerase II, and eukaryotic transcription typically requires disruption of a repressive chromatin context (*1*). The recruitment of transcription factor IID (TFIID)[1] to the promoter is a critical component of both of these processes, and it can be rate-limiting in transcription (*2*). Making a promoter accessible to the transcriptional machinery entails chromatin remodeling by molecular machines such as the SWI/SNF ATPase complex and/or histone acetylation by factors such as p300/CBP. The actual changes induced in chromatin structure, and therefore the mechanisms by which remodeling potentiates TFIID binding, are not clear (*3*). Remodeling ATPases are able to displace histones onto DNA provided in trans, but they do not completely remove the nucleosome; recent work suggests that they may also act by sliding the histone octamer (*4*). Acetylation is likely to act by altering internucleosomal contacts, as it does not have dramatic effects on the structure of an individual nucleosome (*5*).

In this work, I propose a connection between the small, restrained topological domains in chromatin and the mechanism of TFIID recruitment by chromatin remodeling machines. I review recent experiments on topological changes induced by TBP and TFIID which suggest that a writhe cancellation process in DNA minicircles allows TBP-induced untwisting to affect global DNA topology. A speculative molecular mechanism for writhe cancellation via retraction of intercalating Phe stirrups is offered. These experiments (independent of the detailed mechanism) suggest thermodynamic coupling among chromatin remodeling, DNA topology, and TBP binding. The implications of this coupling and some possible experimental tests are discussed.

TOPOLOGICAL CHANGES INDUCED BY TBP AND TFIID

We recently demonstrated (*6*) that when the TATA box binding protein (TBP) is bound to a series of ∼160 bp restriction fragments, it induces negative supercoiling (ΔLk ∼ −0.3) upon ring closure. The constructs used have the TATA box helically phased against a sequence-directed phased A tract bend. A ∼3 bp increase in the optimum length for cyclization and the appearance of negative topoisomers at some DNA lengths were observed, using constructs with in-phase bends for which no twist change is required to align the two bends in the molecule (*7*). The estimated magnitude of the unwinding is similar to the DNA untwisting observed in crystal structures. This was actually unexpected, as in most plasmid experiments TBP had been shown not to affect DNA topology (see below), and the crystal structures showed that the bound DNA shape should contribute to positive writhe that cancels the negative twist from unwinding (*8, 9*). The overall bending in the structure is composed of two kinks at the edges, caused by two pairs of partially intercalated phenylalanines wedging the minor groove open, and a smooth bend through the center of the TATA box, from relatively uniform roll and unwinding. The central segment

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[1] Abbreviations: TBP, TATA box binding protein; hTBP, human TBP; aTBP *Arabidopsis* TBP; Wr, writhe; Tw, twist; Lk, linking number; PIC, preinitiation complex; TFIID, transcription factor IID; TAF, TBP-associated factor; bp, base pair(s).

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is nearly perpendicular to the upstream and downstream DNA.

Comparison of the minicircle results with previous studies suggests that the observed TBP-induced unwinding is specific to minicircles. Hirose and co-workers demonstrated enhanced binding of TBP to supercoiled DNA and activation of preinitiation complex (PIC) assembly and transcription initiation by supercoiling (*10, 11*). However, their plasmid topological relaxation assays showed only very little unwinding and did not give results independent of the initial level of supercoiling. Improved binding to supercoiled DNA could also be due to bending at the apexes of loops. Lorch and Kornberg (*12*), and more recently Oelgeschläger et al. (*13*), found no evidence for unwinding in plasmid relaxation experiments. Oelgeschläger et al. showed that holo-TFIID (TBP with TAFs, *T*BP-*a*ssociated *f*actors) did induce negative supercoiling under the same conditions, and suggested that this is due to wrapping of the DNA about TFIID, as suggested by their cross-linking and previous footprinting results (reviewed in *14*). Recent low-resolution structures of TFIID suggest that nucleosome-like wrapping of DNA around TFIID does not occur (*15*). Thus, in general, while the situation in plasmids or for TFIID is not clear, one net result of previous work is that a potentially interesting class of models suggesting that TBP and supercoiling could reciprocally affect each other or that TBP-induced untwisting could nucleate strand separation in the transcription bubble fell out of favor.

Differences between plasmids and minicircles can be explained by the idea that in a small, constrained topological domain, the twist/writhe compensation observed in TBP·DNA complexes no longer operates. Instead, since writhe in minicircles requires an energetically unfavorable amount of bending, being in a minicircle form tends to flatten DNA. [Theory confirms that ~200 bp minicircles are not significantly writhed at thermally accessible energies (*16*).] This means that in a minicircle TBP-induced writhe is canceled, unmasking TBP-induced untwisting. The next section suggests how this might occur in detail, but the implications for transcriptional activation discussed in the subsequent section apply irrespective of the origin of net negative supercoiling. They should also apply to holo-TFIID as well as TBP.

SPECULATIVE MOLECULAR MECHANISM FOR TBP WRITHE CANCELLATION IN MINICIRCLES

Twist/writhe compensation originally suggested for TBP and minicircle writhe cancellation proposed here can both be understood using numerical calculations of writhe for minicircles. Writhe is given by the Gauss double integral over the helix axis contour *C*:

$$\mathrm{Wr} = \frac{1}{4\pi}\oint_C\oint_C \frac{(\mathrm{d}\mathbf{r}_1 \times \mathrm{d}\mathbf{r}_2)\cdot\mathbf{r}_{12}}{|\mathbf{r}_{12}|^3}$$

where $\mathrm{d}\mathbf{r}_1$ and $\mathrm{d}\mathbf{r}_2$ are unit tangents at $\mathbf{r}_1$ and $\mathbf{r}_2$ on the axis, and $\mathbf{r}_{12} \equiv \mathbf{r}_1 - \mathbf{r}_2$. The dominant contributions to the writhe of a "figure 8" arise from the four segment−segment interactions near the crossover, leading to the intuitive notion of computing writhe as the number of helix axis crossovers. TBP-induced writhe can be estimated by removing half of a "figure 8" and joining the crossover points to form a "teardrop," leaving only one segment−segment contribution, for Wr = 0.25. This nearly compensates for the twist deficit, explaining TBP's twist/writhe compensation, but it therefore does not rationalize the supercoiling actually observed in minicircles.

Figure 1 shows a possible mechanism for minicircle writhe cancellation, via flattening of the TBP·DNA complex. Flattening has the effect of moving the contributing perpendicular segments of the teardrop away from each other and making them more nearly coplanar, thereby decreasing their contribution to the writhe integral. The connecting segment remains coplanar with each side and thus does not contribute. At the molecular level, the proposed flattening deformation corresponds to progressive retraction of the partially intercalating phenylalanines of the "stirrups" of the TBP·DNA interface, removing the large roll kinks observed at the edges of the TATA box, at sites indicated by the carets: T^ATAAAA^G (*8, 9, 17*). The models in Figure 1 show the consequences of this change: the overall bend angle is essentially unchanged, the TBP is rotated relative to its initial position, and the complex is flat and slightly extended. (This surprising result arises because the original structure has about 180° of local bending, with the kinks oriented perpendicular to bending induced throughout the open minor groove of the TATA box; kink removal leaves the minor groove bending intact.) The proposed rotation of TBP would alter the face of the DNA helix available to other factors such as the TAFs or TFIIB; we suggest that protein flexibility in holo-TFIID would still support binding, and the other general transcription factors have only limited sequence specificity. The TBP stirrups would need to move away from the DNA to avoid steric conflicts with the new shape, but no change in the protein−DNA interface over the center of the TATA box is required, and no change in the local twist is introduced.

If the proposed site flattening occurred in a minicircle, the twist change over the site would be unchanged but the positive writhe contribution from the segment would be decreased, requiring a compensating change (overtwisting) in the rest of the molecule to maintain an integral linking number, as Lk = Tw + Wr. The stirrup retraction model could be tested by mutation of the intercalating Phe residues in TBP: relative to wild type, mutants should bind much better to supercoiled minicircle templates than to linear templates, bind with reduced specificity for the terminal base pairs of the TATA box, and induce the same ΔLk in minicircles.

There is other experimental evidence suggestive of multiple TBP·DNA conformations. Time-resolved fluorescence energy transfer measurements on the slow formation of the TBP·DNA complex identified intermediate states, some of which are populated at equilibrium, which all contained bent DNA (*18*). An intrinsic TATA box bend is directed opposite to the TBP-induced bend, and we have suggested that bend inversion may be a slow step in binding (*6*). Spectroscopic studies may be able to identify a change in bend orientation, and time-resolved studies of binding to minicircle topoisomers would show whether topological changes affect the rate-limiting steps. Also, TBP binding to pre-bent minicircles is enhanced as expected when the induced bend is in-phase with sequence-directed curvature, but an out-of-phase bend

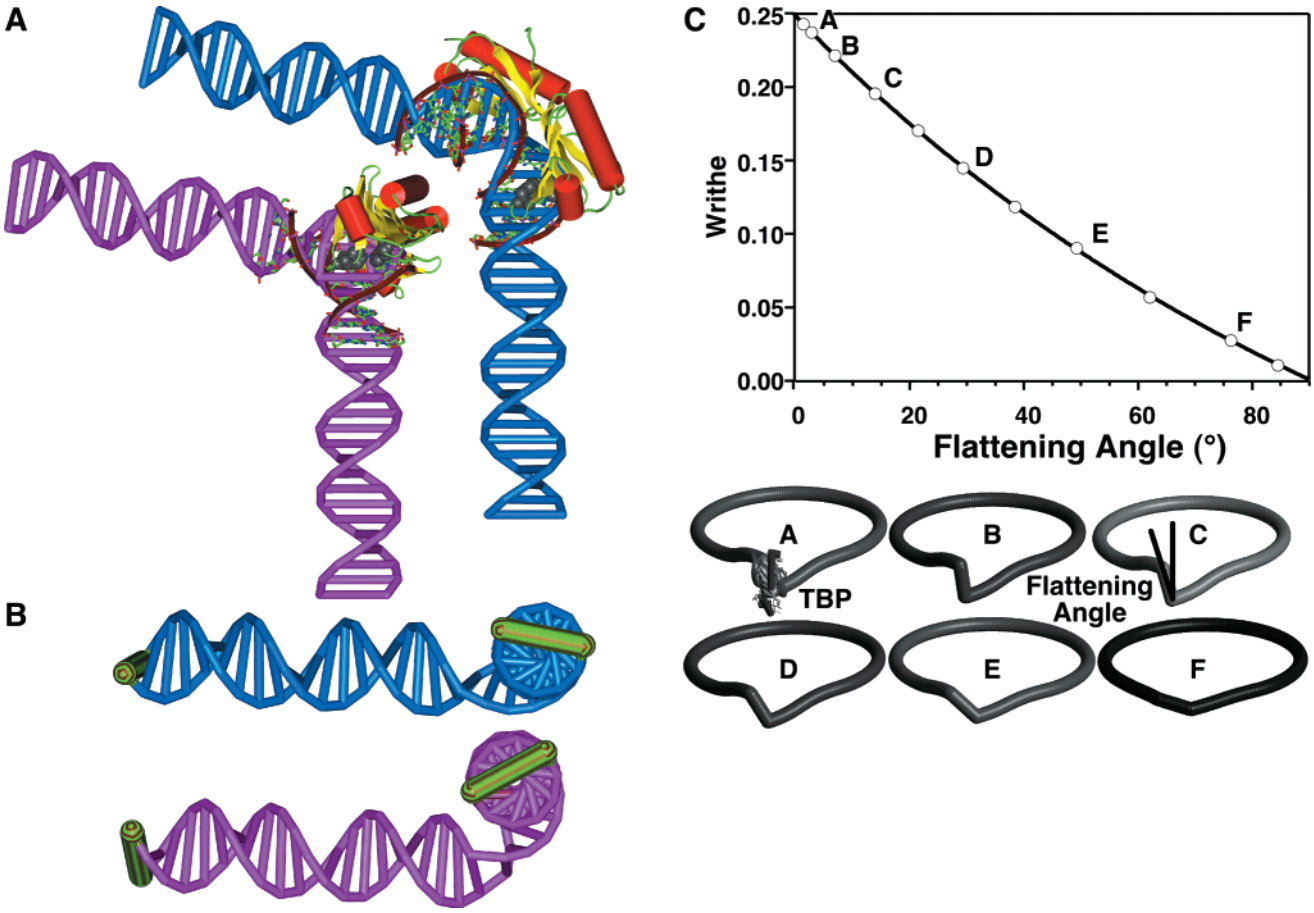

FIGURE 1: Speculative TBP stirrup retraction mechanism for writhe cancellation through minicircle flattening. Panels A and B: The structure of hTBP·DNA (*17*) is superimposed on low-resolution models generated from DNA roll, tilt, and twist angles as described (*7*). The purple DNA is generated using smoothed aTBP·DNA angles (*9*). The blue DNA shows the consequences of stirrup retraction, generated by setting the roll angles at the two Phe kinks equal to zero but otherwise leaving all angles unchanged. Panel A shows that the overall bend angle is remarkably unaffected by retraction; rather, the long-range effects are to rotate the helical phase of the surrounding DNA relative to the bend and to extend the DNA slightly. Panel B illustrates flattening. Thick green bars represent the DNA torsional phase, showing that flattened DNA embedded in a planar circle requires increased twist outside the fragment shown. Thus, writhe cancellation (global reduction of ΔWr upon flattening) leads to compensating positive ΔTw to maintain an integral Lk, canceling negative superhelical tension in the DNA outside the bound region. Panel C: Varying extents of writhe cancellation, calculated as a function of flattening angle by numerical integration in Matlab (The Mathworks, Inc.). The flattening angle is approximately 90° (the sum of the two Phe kink roll angles), for equal kink angles. The figure was rendered in Insight II (MSI) from space curves generated in Matlab.

has surprisingly little repressive effect (*19*): this could be due to the change in rotational orientation seen in Figure 1 (or from binding in-phase nonspecific sites). Similarly, there is surprisingly little repression of cyclization due to out-of-phase TBP-induced and sequence-directed bends (*6*); this was interpreted as incomplete occupancy, but it could also be due to TBP plasticity under strain.

Variability of the TBP writhe contribution could allow TBP to act as a "supercoil shock absorber", allowing the binding response to be consistent over a range of supercoiling. TBP could absorb from 0 to −0.3 of linking number deficit into untwisting by varying the extent of stirrup retraction and writhe cancellation (see Figure 1C). TBP could prevent propagation of torsional strain into neighboring chromatin, perhaps reducing disruptive long-range effects of transcription [Hoffmann et al. (*14*) have proposed that holo-TFIID acts like a nucleosome in regulating access to promoter DNA.] Note that if TBP in fact induces topological changes at all DNA lengths, this would argue against the shock absorber model, which requires the ability to vary ΔWr. Experiments on the length dependence of TBP- and TFIID-induced supercoiling are in progress.

How general might writhe cancellation and supercoil shock absorbers be? The detailed mechanism above is unique to TBP, but any protein which can bind wrapped or twisted conformations with similar affinity could be capable of the same function. Small DNA binding proteins which introduce planar bends would not be able to do this. Among larger complexes, RNA polymerase is a candidate. Writhe converts to untwisting during open complex formation (*20*), and the relationship between transcription and upstream DNA bending has been discussed in terms of vibrational conversion of writhe and twist (*21*). It is suggestive that measurements of open complex-induced unwinding in minicircles [(*22*), (*23*), and J. Jenssen, V. Vittal, and J. D. Kahn, unpublished results] have given ΔLk ~ -1, less than the ΔLk ~ -1.7 seen in plasmids (*24*) but comparable to the extent of single-stranded DNA in the open complex. The nucleosome is a second candidate shock absorber: nucleosome reconstitution on minicircles can give different ΔLk's, and this may reflect changes in the DNA crossover geometry after DNA exits the nucleosome (*25*). The ΔLk from remodeling may give a topology near the buckling critical point (*26*), making the final DNA

structure sensitive to sequence or to binding of additional proteins.

THERMODYNAMIC LINKAGE BETWEEN CHROMATIN REMODELING AND TBP BINDING

Chromatin remodeling induces topological changes, which can be detected by topoisomerase relaxation assays on plasmids. The normal ΔLk/nucleosome of −1 becomes less negative upon remodeling or acetylation, as released negative supercoiling is removed by the topoisomerase. In vivo measurements in yeast have shown that remodeling releases ΔLk ∼ +0.7 per nucleosome on minichromosomal templates (*27*), and acetylation of H3 and H4 in reconstituted minichromosomes reduces nucleosome stability and gives ΔLk ∼ +0.2 per nucleosome (*28*).

I suggest that supercoiled minicircles provide a useful model system for remodeled DNA in a chromatin context. Diffusion of induced supercoiling changes in chromatin into the neighboring nucleosomes requires nucleosome rotation or changes in the helical phasing of DNA on the face of the nucleosome, and this is expected to retain supercoiling in the local topological domain for some time after remodeling (*26*). Since our minicircles are similar in size to a nucleosomal repeat, the physical consequences of a given ΔLk may be similar as well. The results above on TBP binding suggest that remodeling-induced topological changes per se may be directly responsible for TFIID recruitment, in addition to the role of remodeling in making chromatin sites accessible to DNA binding proteins (*29*, *30*). The ability of TBP to bind to nucleosomal DNA is controversial, but SWI/SNF or acetylation clearly enhance binding (*30*, *31*).

Thermodynamic coupling enhanced TBP binding to chromatin remodeling is inferred from the coupling of supercoiling to binding: since TBP induces negative supercoiling, it must bind better to negatively supercoiled DNA, just like ethidium bromide. Figure 2 illustrates this coupling: chromatin remodeling or histone acetylation frees some of the nucleosomal supercoiling, which is localized in a constrained region of DNA bounded by attachment to the rest of the chromatin fiber (*26*). Then, TBP binding to the torsionally strained DNA relaxes some of the supercoiling by canceling some of the untwisting, and thus there is a driving force for enhanced binding. In Figure 2, for emphasis, all of the nucleosomal supercoiling becomes available as writhe, whereas actually it would be largely in twist and there would be a smaller ΔLk. If holo-TFIID induces additional bending or writhe, more of the released supercoiling would be taken up and this would further enhance binding.

Topological coupling has several implications. It is independent of protein−protein-mediated mutual recruitment of TFIID and remodeling machinery, as proposed for cooperative binding by independent DNA binding proteins which compete with the nucleosome (*32*). A nucleosome positioned over the TATA box excludes TBP, and upon activation the nucleosome may be displaced by TFIID (*33*); if TBP then absorbs some of the released supercoiling, nucleosome rebinding should be inhibited. Topology-driven binding would apply to TATA boxes which had not been occluded but were in the same topological domain as a remodeled nucleosome. Conversely, the energetic cost of inducing supercoiling without prior remodeling will contribute to maintaining the repressed state throughout the domain, consistent with observations on repression of internucleosomal TATA boxes (*34*). The position of TBP-induced bending within the domain could modulate the effect due to twist changes required to maintain planarity (*7*, *35*) or to strain in the rest of the domain from accommodating multiple bends (*36*).

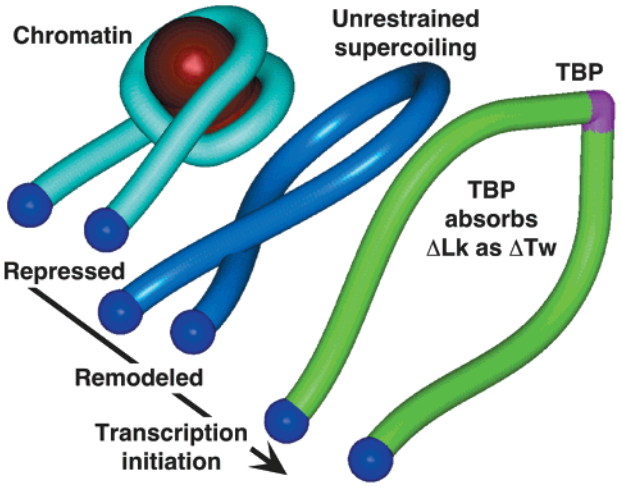

FIGURE 2: Proposed thermodynamic coupling of chromatin remodeling and TBP binding. Repressed (nucleosomal) chromatin (cyan DNA around a brown histone core) is remodeled, and disruption of histone−DNA or inter-histone contacts releases unrestrained negative supercoiling, shown appearing as writhe (blue DNA). Dark blue termini represent fixed attachment sites to neighboring chromatin. TBP (not shown, binding the TATA box in purple) acts as an unwinding ligand in the context of restrained DNA. Decreased negative ΔLk (to give the green DNA on the right) is a thermodynamic driving force enhancing TBP binding to negatively supercoiled DNA, independent of changes in TATA box accessibility. Rendered as in Figure 1.

Binding enhancement should be transient, as the topological driving force from unrestrained supercoiling will dissipate in a possibly regulated manner: in vivo experiments on plasmids assembled into chromatin in yeast suggest that altered supercoiling is rapidly relaxed (*37*), but supercoiled domains can also be stably maintained (*38*) and remodeling may induce long-lasting changes (*29*, *39*). Time-dependent enhancement could provide a pulse of transcription initiation in response to a stimulus, even in the absence of nucleosome reassociation, leading to more rapid induction of gene expression. In contrast, enhanced TBP binding due to TATA box accessibility should persist as long as the nucleosome does not re-form. Due to the long lifetime of TFIID·TFIIA·DNA (*40*), reinitiation of transcription may be less sensitive to supercoiling, as suggested by experiments showing a lack of effect of template linearization in yeast (*41*). As in many connections between supercoiling and transcription, effects on reinitiation are possibly complex. If topoisomerase action relaxed TBP-induced negative supercoiling, it could destabilize TBP binding and halt reinitiation. On the other hand, transient negative supercoiling induced by polymerase movement could retain TBP and maintain high-level transcription, while TBP as a shock absorber could prevent propagation of supercoiling upstream. Similar functions have been ascribed to sequence-specific single-strand DNA binding transcriptional activators (*42*).

POSSIBLE EXPERIMENTAL TESTS OF TOPOLOGICAL COUPLING

If the proposed coupling mechanism is significant in vivo, it must have detectable consequences for the rate or efficiency of transcriptional activation or repression. The model predicts that the binding of TBP to a small topologically closed domain will be inhibited by a positioned nucleosome even if the TATA box is not occluded, and that remodeling will allow binding, which is readily tested in vitro. It predicts that TBP binding and transcriptional activation on recently remodeled DNA will be enhanced, and that as the unrestrained supercoiling dissipates by diffusion or is removed by topoisomerases the enhancement will decrease even if the TATA box remains accessible. This could be tested in vitro by order-of-addition experiments, for example, measuring TBP binding as a function of time after SWI/SNF addition to a minichromosome template. Similar measurements in vivo would be challenging because of the difficulty of controlling the timing of remodeling and TBP availability, but, for example, the model predicts that TBP binding to remodeled chromatin would be potentiated under conditions where topoisomerases are inhibited, or that remodeling a large chromatin stretch would paradoxically make the region a poorer partner for TBP due to dispersion of supercoiling.

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