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Opinion

Disentanglement of DNA in the Eukaryotic Nucleus

Raul A. Saavedra[1,*,§]

[1]The author is a retired scientist that has held positions at The California Institute of Technology, Harvard Medical School, Boston Children's Hospital, Medical College of Pennsylvania and The National Institutes of Health, USA. Currently the author is not affiliated with any institution

*Correspondence: rsaavedra1@earthlink.net (Raul A. Saavedra)

[§]Retired.

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Abstract

In the eukaryotic nucleus, the establishment and maintenance of DNA topological states depend on the complex interplay of nucleosomes, topoisomerase enzymes, DNA transactions, and environmental temperature. This article describes and integrates the roles of these participants in this intricate yet fascinating biological phenomenon.

Keywords: topology; nucleosomes; topoisomerase; temperature; evolution

1. A Brief Introduction to DNA Topology: The Intricate Case of Eukaryotes

The DNA double helix exhibits significant flexibility, allowing the helix to adopt a wide range of conformations. Why, then, does the engagement of DNA molecules in multiple transactions not lead to entanglement, the formation of inextricable knots, and disruptions in the informational flow of the cell? Throughout evolution, organisms have resolved these potential difficulties through the emergence of several mechanisms that help preserve the topological integrity of molecules [1,2]. In cells, DNA is topologically constrained, *i.e.*, the two strands of the molecule cannot be completely separated from one another unless a break is introduced into one or both of the strands. DNA can become topologically constrained through direct covalent linkage of the ends, as in plasmids and mini-chromosomes (Fig. 1; Ref. [3]). DNA can also be constrained by the anchoring of two distinct regions of the molecule. This is the case in chromosomes, where protein complexes called structural maintenance of chromosomes (SMC) complexes, such as condensin, extrude DNA loops to organize the three-dimensional architecture of a chromosome [4,5]. The number of times one DNA strand passes over the other is called the linking number, which equals the number of twists plus writhe. The latter corresponds to the amount of positive and/or negative supercoiling, the sign of which depends on right- or left-handed spatial rotation.

In living organisms, cellular processes and extracellular stimuli, such as environmental temperature, can generate DNA supercoils of both signs in at least a fraction of their genomes, thereby producing torsional tension, a form of mechanical energy [2,5]. The energy stored in some supercoils can be utilized in the same processes, but most supercoils are removed to maintain the topological state and proper cellular function. The overall mechanisms that generate and maintain DNA topology in the eukaryotic nucleus are similar to those found in other evolutionary domains of life, such as bacteria and archaea. Nevertheless, differences arise from the emergence of some mechanisms and the apparent loss of others during evolution. This is the case with the presence of nucleosomes [6,7] and the absence of a DNA gyrase-like topoisomerase in the eukaryotic nucleus [8]. The absence of DNA gyrase activity in the eukaryotic nucleus raises the question of how negative supercoils are generated and maintained in eukaryotes. The answer lies in a distinct topological DNA scenario in the eukaryotic nucleus; this framework involves a complex interplay among nucleosomes, topoisomerase activities other than gyrase, genomic transactions, and environmental temperature. This article discusses the roles of these factors in eukaryotic DNA topology, with special emphasis on the contribution of environmental temperature.

2. The Nucleosome: An Essential Partaker in the Maintenance of Eukaryotic DNA Topology

The basic unit of eukaryotic chromatin is the nucleosome. X-ray studies show that each eukaryotic nucleosome consists of 147 base pairs (bp) of negatively supercoiled DNA wrapped 1.65 times as a flat superhelix around a core of histone proteins [6,7]. The nucleosome core exhibits a specific arrangement of histones that fold onto one another to form a flattened cylinder that defines a path for the supercoiled DNA molecule. Topological studies of mini-chromosomes indicate that there is ~1.0 negative supercoil per nucleosome (Figs. 1,2, Ref. [3]). To reconcile the discrepancy between X-ray and topological studies, a proposal has been presented that the linking number per nucleosome depends on (1) the number of bp separating one nucleosome from another and (2) the degree of compaction that distinguishes active from repressed chromatin [9].

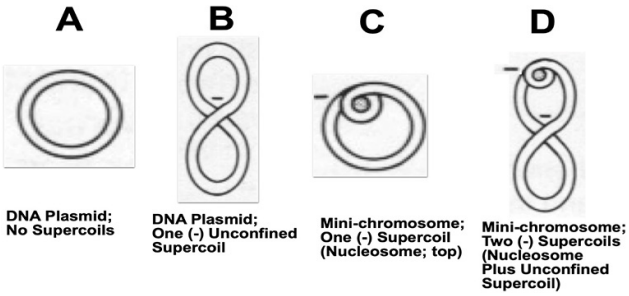

Fig. 1. Topologically constrained DNA molecules. (A) A topologically constrained DNA molecule (plasmid) with no supercoils. (B) A topologically constrained DNA molecule (plasmid) with one unconfined negative (-) supercoil. (C) A topologically constrained DNA molecule (mini-chromosome) with one confined negative (-) supercoil wrapped around a nucleosome core (gray circle) to form a nucleosome (top). (D) A topologically constrained DNA molecule (mini-chromosome) with one confined negative (-) supercoil wrapped around a nucleosome core and one unconfined negative (-) supercoil; modified from Fig. 1 of Ref. [3] with permission from Cell Press (Elsevier).

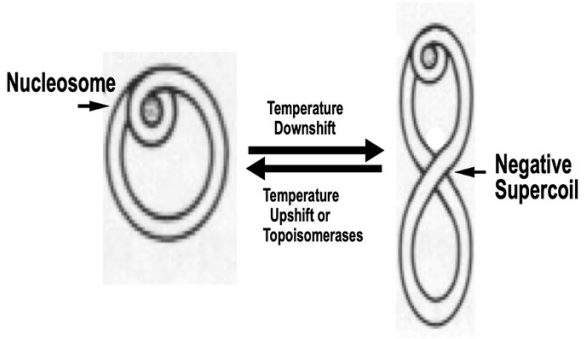

Fig. 2. Schematic representation of the effect of temperature on a eukaryotic (yeast) mini-chromosome. (Left) A eukaryotic mini-chromosome containing one nucleosome. (Right) A temperature downshift generates unconfined negative supercoils within an amenable segment of the DNA molecule. The number of supercoils generated depends on the extent of the temperature shift. This topological change in DNA can be reversed by a temperature upshift or by active DNA topoisomerases. The nucleosome includes the core (gray circle) and ~1.0 negative supercoil wrapped around the core. The actual effect of temperature on the topology of nucleosomal DNA requires further investigation. Modified from Fig. 1 of Ref. [3] with permission from Cell Press (Elsevier).

Each eukaryotic histone contains a well-organized central domain and less organized amino- and carboxyl-terminal tails. X-ray studies show that the nearly parallel orientation of the DNA superhelical turns permits the alignment of the associated minor grooves to form channels through which some of the amino and carboxyl tails exit the nucleosome [10]. Thus, pairs of histone tails further stabilize the nucleosome structure by embracing the DNA molecule at defined intervals along the superhelix. Therefore, the DNA superhelix in the classical nucleosome exhibits rather limited amenability to topological alterations. Although the nucleosome is a thermodynamically stable structure, the nucleosome can also display a dynamic behavior due to the existence of histone variants [5] and the numerous post-translational modifications that occur in histones. Furthermore, nucleosomes can be disassembled and reassembled through specific molecular mechanisms to maintain DNA topology and other nuclear functions.

3. Topoisomerase Enzymes: The Biochemistry, the 'Missing' Topoisomerase, and Genomic Topological Homeostasis in Eukaryotes

Topoisomerases constitute a large, ancient, and essential family of enzymes that catalyze topological alterations of nucleic acids and are present in all three domains of life [11,12]. In the case of DNA, these enzymes alter topology through the concerted breakage, passage, and rejoining of the two strands. The major subfamilies of topoisomerases are topoisomerase I (Topo I) and topoisomerase II (Topo II). Type I enzymes require Mg^{2+} for DNA relaxation activity, whereas Type II enzymes require Mg^{2+} and ATP hydrolysis as an energy source. Topoisomerases cleave the phosphodiester backbone of the DNA molecule by forming a transient covalent bond between a tyrosine residue of the enzyme and the DNA 3′ end in the case of Topo I or the 5′ end in Topo II [12] Resealing of the break is performed via a nucleophilic attack by the 5′-hydroxyl end in Topo I and the 3′-hydroxyl end in Topo II.

Eukaryotic organisms seem to lack a nuclear gyrase-like topoisomerase, such as the Type II enzyme that participates in the generation and maintenance of negative supercoils in prokaryotic and archaeal cells [1,13]. An initial indication consistent with this premise was the observation that the naturally occurring 2-micron mini-chromosomes of the yeast *Saccharomyces cerevisiae* were not substrates for a gyrase-like topoisomerase *in vivo* [3]. Subsequent observations further supported this premise. Genes that code for DNA gyrase are found in the nuclear genome of the plant *Arabidopsis thaliana* [8]. However, the corresponding gene products are exported to mitochondria and chloroplasts. The nuclear genome of the parasite *Plasmodium falciparum* also contains genes encoding gyrase, whose products are exported to the apicoplast, a vestigial chloroplast-like organelle [14]. In mammals, there are at least four mitochondrial topoisomerase enzymes, all encoded in the nuclear genome [15]. Interestingly, the human genome also contains a related gene encoding proteins that could, in principle, be targeted to the nucleus and mitochondria; however, a nuclear gyrase-like activity has not yet been reported.

The evolutionary point at which the eukaryotic nucleus lost gyrase activity remains uncertain. Since 'prim-

itive' eukaryotes, such as yeast, do not exhibit this nuclear activity, one can envision that the loss of activity occurred early in eukaryotic evolution, possibly close to the time when eukaryotes diverged from archaeans (conservatively estimated between 2.2 and 1.5 billion years ago (bya)) [16]. Instead, the eukaryotic nucleus contains topoisomerase activities that remove both positive and negative supercoils. The presence of topoisomerases that primarily remove supercoils, together with other participants, has established a distinct framework for the regulation of topological homeostasis in the eukaryotic nucleus. While some transactions, such as transcription and replication, and physical stimuli, such as environmental temperature, generate positive and negative supercoils, other processes remove these coils. Various topoisomerase activities remove a significant number of positive and negative supercoils; moreover, positive and unconfined negative supercoils can cancel one another. Furthermore, nucleosomes confine negative supercoils, thereby helping preserve the overall topological state of the eukaryotic genome.

4. Eukaryotic Transcription and Replication: Significant Generators of Supercoils

Once a transcription initiation complex binds to a promoter sequence, separation of the two DNA strands generates a 'bubble' that grows as the displacement of the complex moves along the DNA molecule. Several events follow: (1) elongation of the nascent RNA molecule, (2) generation of positive supercoils in front of and negative supercoils behind the advancing complex, and (3) displacement, disassembly, and reassembly of nucleosomes (nucleosome turnover) [2,15,17]. The accumulation of positive supercoils in front of the complex could eventually halt progression if the coils are not promptly removed or canceled. These positive supercoils are removed mainly by Topo I and Topo II enzymes. The torsional energy of these positive supercoils can also facilitate the displacement or disassembly of downstream nucleosomes. These disassembled nucleosomes generate unconfined negative supercoils (Figs. 1,2), which positive supercoils could cancel. The negative supercoils generated behind the complex are removed mainly by Topo I [2,15]. Some of these supercoils can also contribute to the reformation of nucleosomes disassembled by the advancing transcription complex.

Similar topological phenomena occur during DNA replication, except that this process involves the entire cellular genome [2,15]. As replication proceeds bidirectionally, the advancing complexes form a bubble that expands in both directions. Positive supercoils form in front of, and negative supercoils form behind, the advancing complexes at both ends of the bubble. The positive supercoils generated in front of the complexes are removed by Topo I and Topo II enzymes. Another mechanism proposed to relieve the torsional tension generated by the replication complex involves rotation of the advancing fork. This rotation generates DNA catenates behind the fork, which Topo II must remove before replication is completed [18]. Some of the positive supercoils can also contribute to the cancellation of unconfined negative supercoils generated by disassembled nucleosomes in front of the advancing complexes. Most negative supercoils formed behind the complexes are removed mainly by Topo I and Topo II. The remaining negative supercoils can be utilized in the reformation of nucleosomes disassembled by the advancing replication complexes and in the formation of new nucleosomes behind the forks. In the final stages of replication, the daughter DNA molecules are separated from one another by a process involving Too II. Thus, replication leads to duplication of the eukaryotic genome and preservation of the overall topological state.

5. The Often-Overlooked Effects of Environmental Temperature: The Role of Environmental Temperature in the Ecological Adaptability and Evolution of Eukaryotes

The effects of environmental conditions, such as temperature, on DNA topology have been understudied. Notably, double-stranded DNA molecules respond to decreases in temperature by becoming more tightly wound and increasing the angle between neighboring base pairs. In topologically constrained DNA, this increase in twist is compensated for by an increase in negative supercoils (Fig. 2) [3]. Conversely, topologically constrained DNA responds to increases in temperature by reducing twist and increasing positive supercoils. These phenomena can be observed in naked DNA molecules as well as in living organisms across all evolutionary domains. The extent of the cellular DNA response depends on two main variables: (1) the temperature difference experienced by the organism and (2) the fraction of cellular DNA amenable to topological alterations. The latter depends on the degree of chromatin compaction, with lower compaction implying a greater topological response. Unicellular eukaryotes constitute a group of convenient experimental models for investigating these topological phenomena *in vivo*, particularly through studies of the associated extrachromosomal elements. For instance, a temperature change from 38 ℃ to 0 ℃ generates an increase of ~5 negative supercoils in the 2-micron mini-chromosomes of *S. cerevisiae*; thus, ~70% of this mini-chromosomal DNA is amenable to topological alterations. The resulting supercoils are relaxed by the combined activity of Topo I and Topo II [3]. Synthetic mini-chromosomes, such as TRP1ARS1 and GAT2, when transfected into *S. cerevisiae*, respond similarly to temperature changes [19]. An intriguing finding from these studies is that the DNA of yeast mini-chromosomes exhibits a greater topological response to temperature changes than mini-chromosomes reconstituted with chicken histones [19]. One possible explanation for this difference is that DNA–histone interactions differ in yeast from those in higher eukaryotes. These differences may reflect the expansion of nuclear genome

size and complexity during eukaryotic evolution, ranging from 2.3 Mbp in a microsporidian to more than 10^5 Mbp in some plants [20], as well as the need to regulate gene expression and the topology of increasingly large genomes. Further investigation could lead to an improved definition of the fractions of genomic DNA amenable to topological responses to temperature in lower and higher eukaryotes.

These DNA properties could have important ecological and adaptive significance. Eukaryotes, including protists, have expanded into a variety of hostile environments. These include deserts, where temperatures can fluctuate significantly during 24 hours, as well as hot or cold habitats with extreme but less variable temperatures. The Coastal Cordillera Region of the hyperarid Atacama Desert is inhabited by protist species of the Cercozoan clade that survive severe desert conditions [21]. At one end of the temperature spectrum are hot springs inhabited by protists such as the primitive red alga *Cyanidioschyzon merolae*, which tolerates temperatures of 60 ℃ [22]. At the other end of the spectrum are cold environments, such as those in Antarctica, where the diatom *Fragilariopsis cylindrus* endures temperatures of –20 ℃ [22]. The extreme temperatures at which some protist species can survive raise the possibility that these organisms possess modified or novel topological activities. Such hypothetical mechanisms could enable the survival of some protists at high temperatures, perhaps analogous to reverse gyrase, the DNA topoisomerase that introduces positive supercoils in hyperthermophilic archaea [23]. Other potential constituents could contribute to the homeostasis of eukaryotic DNA topology under severe cold conditions, thereby supporting the wide distribution and adaptability of eukaryotes.

Environmental temperature has played a critical role in the distribution of eukaryotic habitats and may also have influenced their evolutionary origins. Eukaryotic organisms diverged from archaea around the time of the Great Oxygenation Event (2.2–1.5 bya) [16]. Comparisons between eukaryotic and archaeal chromatin structures offer some insight into this still-puzzling process. When eukaryotic nucleosomes are compared with the associated archaeal counterparts (archaeosomes), an interesting picture emerges [6,24]. Archaeosomes from archaea *Methanothermus fervidus* exhibit an overall architecture similar to that of nucleosomes, but they also show significant biochemical differences. Archaeosomes contain two histone-like proteins (HMf1 and HMf2); these proteins are smaller than eukaryotic histones and can form homo- and heterodimers. There are also topological differences between these two structures, whereby instead of the 147 bp of DNA wrapped around nucleosome cores, archaeal nucleosome cores can continuously wrap between 60 and 500 bp. Analysis of HMf2 homodimers indicates that archaeosomes are arranged in a ‘slinky-like’ fashion, exhibiting more dynamic (quasi-stochastic) behavior [24]. Fascinating topological studies have been conducted on extremophilic archaea, including species in the clades Sulfolobus and Thermococcales [25]. These studies have established a close relationship among temperature, DNA topology, and topoisomerases, which enables these organisms to survive under extreme environmental conditions (85 ℃ to 100 ℃). Advances in research on archaeal organisms and the recent proposal that the origin of eukaryotic chromatin may be related to that of extreme thermophilic archaea [26] make the study of eukaryotes living at high temperatures a compelling priority.

6. Conclusions and Future Challenges

The preservation of DNA topology is essential to the survival of all organisms. The mechanisms that preserve DNA topology in the eukaryotic nucleus are similar to those found in organisms from other evolutionary domains; nevertheless, some important differences exist. Among these are the essential roles of nucleosomes, the absence of a DNA gyrase-like topoisomerase, and the presence of topoisomerases that mainly remove positive and negative supercoils in the eukaryotic nucleus. These differences lead to a somewhat distinct topological scenario in the nucleus of eukaryotic cells. Environmental temperature also plays a critical role in the generation of DNA supercoils; moreover, environmental temperature has played a major part in the widespread ecological distribution of eukaryotes and, possibly, in their evolutionary origin.

The flexibility of eukaryotic chromatin is critical to the associated function in DNA transactions and subsequent responses to environmental temperature. Several mechanisms that contribute to the stability and dynamics of nucleosomes are well understood at various levels. However, a better understanding of transitions between chromatin states would benefit from further *in vivo* analyses of DNA–nucleosome core interactions [9,27]. These studies will help elucidate several issues related to the dynamic behavior of eukaryotic chromatin, including the mechanism(s) underlying the different temperature responses exhibited by lower- and higher- eukaryotic chromatin [19]. Studies on the effects of environmental temperature on eukaryotic DNA topology clearly lag behind other aspects of chromatin research. In particular, more topological and biochemical studies are needed on eukaryotic microorganisms living in extreme habitats, such as the thermophilic protist *C. merolae*, which inhabits hot springs [22]. These investigations are timely in light of the compelling proposal that the origin and evolution of eukaryotic chromatin may be related to those of extreme thermophilic archaea [26]. Such conceptual and experimental investigations will lead to a deeper understanding of the maintenance of eukaryotic DNA topology and the associated roles in the physiology, ecology, and evolution of these organisms.

Author Contributions

RAS prepared the figures, conducted the literature search for the manuscript and wrote the paper. RAS has

participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author declares no conflicts of interest.

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