The emerging role of DNA supercoiling as a dynamic player in genomic structure and function

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Abstract This editorial highlights the pervasive role of DNA supercoiling in genomic structure and function and introduces the main themes of the reviews in this Special Issue.

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DNA supercoiling is an underlying regulatory feature of the genome of every living system. This Special Issue on “DNA supercoiling, protein interactions and genetic function” is a collection of contributions from scholars in the field who, starting from different backgrounds and using different approaches, have investigated how DNA supercoiling shapes and mediates the interaction of the genome with proteins that manage its genetic information. The emerging view is that DNA is not simply an object to be decoded but is, in fact, a malleable and dynamic substrate that plays an active part in the decoding process. As stated by Travers and Muskhelishvili and endorsed by Levens, Baranello and Kouzine in this Special Issue, DNA contains both digital and analog information. The digital information is in the DNA discrete base-pair sequence, while analog information is provided by the constantly modulated conformation of its continuous physical structure. DNA

supercoiling, be it topologically anchored by proteins or freely diffusing, is dynamic and a major actor in determining short- and long-range genome structure, packaging and, ultimately, accessibility. But where does DNA supercoiling originate from? In both bacteria and eukaryotes long-range DNA superhelicity is mostly due to the activity of DNA translocases, with DNA gyrase also a player in bacteria. These molecular motors inherently generate gradients of opposite superhelicity upstream and downstream of their site of activity. These gradients introduce structural heterogeneity which, in addition to that due to the DNA base-pair composition, affects the binding of proteins, directing some to the unwound and others to the overwound DNA segments. Such time- and location-dependent preferential binding of proteins may constitute an essential driver of chromatin organization. Furthermore, torsional stress can induce other forms of non-canonical DNA which may facilitate a variety of transactions and signal transduction events. This underscores what Levens, Baranello and Kouzine refer to as the ‘material science’ aspect of DNA. They argue that “Evolution has not just accommodated, but has exploited the physical and chemical properties of DNA in service of the programs encoded digitally in the DNA sequence.” This is the new paradigm for DNA, and the genome.

Stark examples of the notion that DNA supercoiling is both a product of DNA–protein interactions and a modulator of the activity of DNA-binding enzymes are those of the nucleosome and of protein-mediated loops. Ordu, Lusser and Dekker review nucleosome dynamics, highlighting the fact that even topologically constrained supercoiling is not static. From the newly measured ‘gaping’, where the coils of DNA on the histone octamer surface move closer and farther apart in time, to the fluctuations of intact nucleosomes and the ‘handedness flipping’ of tetrasomes obtained after loss of the H2A and H2B histones, supercoiling is transferred along the genome. Thus, as Corless and Gilbert also point out, even linker DNA

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may have unconstrained supercoiling. Finzi and Dunlap, after showing the effect of DNA elasticity on protein-mediated loops, argue that because negative supercoiling stabilizes loop-based genetic switches, it is likely to act as a switching signal.

DNA–protein complexes, similar to nucleosomes and genetic switches, may be roadblocks for translocases but, as many contributors in this Special Issue remind us, the waves of supercoiling generated by these molecular machines help the remodeling of chromatin. In fact, Corless and Gilbert, who used psoralen intercalation and cross-linking to map the distribution of negative supercoiling, state that “DNA supercoiling at the level of the gene can alter the state of chromatin around transcribing RNA polymerase at a distance of several kbps.”

Without a question, a lot is known about the effect of DNA supercoiling on transcription. For example, Ma and Wang used an angular optical trap to show the torsional stress generated by a single RNA polymerase (RNAP) molecule which would stall the enzyme to be ~ 11 pN nm. This torque is sufficient to convert DNA into a plectonemic state or to substantially modify chromatin topology. Thus, these results establish RNAP as a powerful torsional motor and support the concept that the torque-generating capacity of RNAP may be tuned to important transitions in DNA or chromatin structures. Indeed, the evolutionary implications of the physical characteristics of these genomic motors are captured by Dorman’s review which directly addresses the relationship between supercoiling, bacterial evolution and pathogenesis. A statement in Dorman’s abstract is particularly telling, “The unwinding of DNA by the ATP-dependent topoisomerase DNA gyrase creates a continuum between metabolic flux, DNA topology and gene expression that underpins the global response of the genome to changes in the intracellular and external environments. These connections describe a fundamental and generalized mechanism affecting global gene expression that underlies the specific control of transcription operating through conventional transcription factors. This mechanism also provides a basal level of control for genes acquired by horizontal DNA transfer, assisting microbial evolution, including the evolution of pathogenic bacteria.”

Ma and Wang’s work also establishes the relevant physiological torque scale for DNA-based processes. The notion that excessive torsional stress stalls RNAPs accounts for transcriptional bursting and links transcription to the activity of topoisomerases, the enzymes responsible for the manipulation of DNA supercoiling. The role of these enzymes in the management of genomic supercoiling is specifically addressed in the two reviews by Seol and Neuman and Higgins, respectively. Seol and Neuman recall that topoisomerases also deal with complications associated with DNA knotting and catenation resulting from repair and replication and review a series

of elegant in vitro experiments aimed at elucidating the mechanisms of various topoisomerases. Focusing on prokaryotic systems, Higgins calls attention to the fact that different bacteria, such as *Escherichia coli* and *Salmonella*, maintain their genomes at a different average supercoiling density and that there is really not a good understanding of why closely related species evolve different optimal supercoil levels and how a given species regulates its supercoil density.

However, more local and perhaps less dynamic changes in the DNA torsional features are introduced at their recognition sites by many DNA-binding proteins. The *E. coli* cAMP receptor protein (CRP) and the lactose repressor (LacI) are excellent examples of this phenomenon, reviewed in this Special Issue by Leng. Given the small scale of the effect, Leng shows that the best approach for studying protein-induced changes in DNA linking number is to construct plasmid DNA templates containing multiple tandem copies of a DNA-binding site for a sequence-specific DNA-binding protein. In addition, he reviews studies that show that supercoiling diffusion out of protein-mediated topological domains is slow, indicating that such domains are effective in maintaining the topology of sections of the genome relatively constant. The work of Perez and Olson helps to visualize these topological barriers and the three-dimensional organization of DNA loops held in place by proteins that bind to widely spaced sites along the nucleotide sequence. The atomic-level simulations of Harris, Noy and Sutthibutpong provide a detailed molecular picture of the diffusion of superhelical stress along the DNA molecule and draw attention to the unique roles of counterions and proteins in influencing both the local and global structure of DNA.

In conclusion, this Special Issue reviews current notions on the regulatory function of DNA supercoiling as well as some of the most incisive approaches that have been used to achieve such knowledge, it conveys the relevance of DNA supercoiling, and we hope it will entice the reader with the many intriguing aspects of DNA supercoiling that are yet to be understood. Citing Higgins, “In the post genomic era, there has been a focus shift from funding research designed to uncover biochemical mechanisms to test genetic relationships to support of correlation science. New fields like proteomics, metabolomics, and translational science are based on a notion that we have sufficient understanding of biological systems that makes it now possible to predict epidemics, solve fundamental problems with massive computational power, and discover cures by developing designer drugs that can target almost any protein target. Daily predictions hint that new work in mouse genetics will lead to cures for everything from diabetes and cancer to Parkinson’s disease. However, there has been little interest in testing the limits of our knowledge.” Much of the work presented

here proves that although there have been tremendous advances and many discoveries, there is still much to be learned about the interplay between DNA supercoiling and essential enzymes like gyrase and condensin, protein-mediated signaling, and the translocases that routinely manipulate the genome. In addition, as Higgins says, researchers who have recently “whittled a larger bacterial genome down to only 531,560 base pairs and

473 essential genes representing the smallest free-living organism, found that >30 % of the genes in this bacterium have no known structure or function.” Thus, abundant and compelling arguments exist for the support of research aimed at understanding biochemical mechanisms, among which DNA supercoiling, also called a barometer of the health status of a cell, a sensor, and a telegraph of cellular signals, is such a pervasive one.