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EDITORIAL

TOPO2008: DNA TOPOISOMERASES IN BIOLOGY AND MEDICINE

The DNA topoisomerases are a group of fascinating enzymes that play an essential but dangerous game with DNA. They break and rejoin either one or both strands of the double helix to solve the problems of tangling and linking that occur as a result of DNA manipulations (replication, transcription and recombination) in all cells. This basic problem with the DNA structure was recognized by Watson and Crick almost as soon as the double helix was described (1). As the parental DNA strands are separated at a replication fork, the double-helical turns are compressed and overwound ahead of the fork; the resulting torsional stress will prevent further replication if it is not relieved. This overwinding corresponds to positive supercoiling. Alternatively, any rotation of the replication fork leads to interwinding of the replicated regions, ultimately resulting in linking (catenation) of the daughter chromosomes, which must be removed if partition is to occur without breaking the DNA (2). Transcription can also result in the generation of both positive and negative supercoiling (3), and other processes, particularly recombination, can lead to the knotting of DNA strands. These complexities of double-helical DNA are grouped together under the label of DNA topology (4). The topological problems of the DNA helix must have arisen very early in evolution, as soon as DNA genomes became long enough that a simple rotation of the entire molecule to remove supercoiling became impracticable.

The only viable solution to these difficulties is to untwist, unlink and unknot the DNA by breaking one or both strands, permitting strands to pass through one another or allowing rotation at the break point. These strategies are adopted by the different classes of topoisomerase enzymes, discovered during the 1970s. The type I enzymes break and rejoin one strand of the helix, and either pass single strands through one another (type IA) or allow one broken end to rotate about the intact strand (type IB). Type I enzymes can remove supercoiling from DNA. In contrast, type II topoisomerases pass one double-helical segment through a double-stranded break in another, in an ATP-dependent reaction, and can thus unlink (decatenate) linked chromosomes, and remove knots. One subset of these enzymes, DNA gyrases, can introduce negative supercoiling (unwinding) into DNA. Most cell types express a suite of topoisomerase enzymes to regulate the topology of their DNA.

However, these manipulations of the DNA helix come at a cost; the broken DNA strands must be efficiently rejoined to avoid serious consequences for the cell. The hijacking of topoisomerase mechanisms to produce stable single-stranded and, particularly, double-stranded breaks is a feature of a wide variety of natural and synthetic chemotherapeutic agents, making the topoisomerase enzymes important drug targets (5,6).

During the 1990s, there were regular meetings on DNA topoisomerases in New York and Amsterdam. However, in recent years these meetings lapsed and we lacked a regular forum to discuss issues concerned with DNA topology and topoisomerases. Happily, Nynke Dekker, Paola Arimondo and Mary-Ann Bjornsti organized an excellent topoisomerase meeting in Fréjus, France in 2007. This re-established the momentum for similar meetings in the future, including Topo2008, which was held last year in Norwich, UK. Tremendous advances are being made in this field, which continues to be a fascinating and vibrant research area. Topics at the meeting ranged from discussions of the intricacies of DNA knotting to the translation of fundamental work on topoisomerases into drug discovery.

This issue of NAR contains a special collection of Surveys and Summaries that cover the field of DNA topology and DNA topoisomerases and reflect the content of the Norwich meeting. Zechiedrich and colleagues discuss how misregulation of topology can lead to cellular dysfunction and consider how cells can prevent such topological problems (7). The control of supercoiling in bacterial cells has been extensively studied; Dorman and Corcoran discuss such studies and the effects of supercoiling on bacterial virulence and infectious diseases (8). Gadelle and Forterre review the origins and phylogenies of these enzymes and suggest that they originated in an ancestral virosphere (9).

Mondragón and colleagues review structural work on type I enzymes, which has led to a deeper understanding of their reaction mechanisms (10). A key feature of many type I and type II enzymes is that they require Mg^{2+} ions in their reaction mechanisms. Sissi and Palumbo discuss the role of Mg^{2+} ions in topoisomerase structure and function, in particular, a proposed two metal ion mechanism for DNA cleavage (11). DNA cleavage in type II enzymes occurs at a region of the enzyme known as the 'DNA gate', and Collins *et al.* describe the use of single-molecule fluorescence energy transfer experiments to probe the dynamics of the DNA gate of type II topoisomerases (12). The double-strand break mechanism for type II enzymes has important implications for the role of topoisomerase II in eukaryotic cells, and Roca discusses the implications of this mechanism in the context of eukaryotic chromatin structure (13).

Bacterial topoisomerase I is a potential, though currently unexploited, target for antibacterial agents; Tse-Dinh discusses screening for novel agents that target this enzyme (14). Deweese and Osheroff consider the DNA breakage–reunion reaction of type II enzymes and how compounds that stabilize the topoisomerase II cleavage complex can act as cytotoxic agents and be utilized as anti-cancer drugs (15).

This collection of reviews illustrates the breadth of research work being carried out in the DNA topology/topoisomerase area, and also highlights some of the unsolved questions that remain. We would like to thank the authors who both participated in the meeting (Topo2008) and contributed to this excellent set of reviews, which will hopefully stimulate further enthusiasm for this field. We anticipate that the next meeting in this series will take place in 2010 in the USA.

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