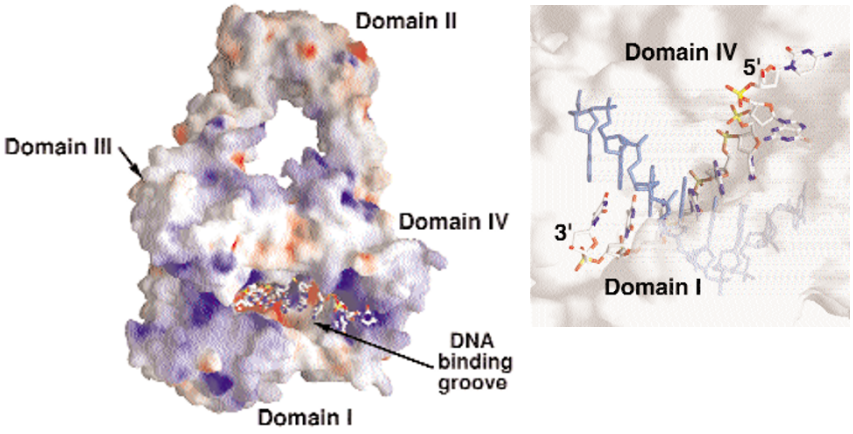
A DNA acrobat



During replication, transcription or recombination, the DNA strands can get tangled up. For example, replication of some bacterial plasmids generates an intermediate with two linked circular DNA molecules that must be resolved to produce two daughter plasmids. In *Escherichia coli*, such a reaction, called decatenation, is catalyzed by topoisomerase III.

Topoisomerase III is a remarkable enzyme. To change DNA topology, it recognizes and cleaves a single-stranded region of DNA and holds and protects both free ends of the broken strand from random ligation reactions that could be detrimental to the organism. Conformational changes in the enzyme result in passing of a second DNA strand or a separate DNA duplex through the break. After DNA passage, the enzyme reseals the break to restore the intact DNA. To understand how topoisomerase III accomplishes these acrobatics, it is necessary to define the structural elements that coordinate this complex multistep reaction.

The crystal structure of an inactive mutant of *E. coli* topoisomerase III in complex with a single stranded octadeoxynucleotide (Changela, A. *et al. Nature*, **in the press**; 2001) now provides some insight. The overall archictecture of topoisomerase III has a toroidal shape (left, shown in molecular surface representation) and can be divided into four structural domains (domain I–IV). The cavity is framed by domains II–IV and is large enough to accommodate either single-stranded or double-stranded DNA, most likely the portion that is to pass through the break. The single-stranded oligodeoxynucleotide in the complex, however, is bound in a groove at the interface of domains I, III and IV (left; DNA shown as a stick model), near the active site of the enzyme. Thus, the structure identifies the site to which the scissile DNA strand binds.

Unexpectedly, the conformation of the single-stranded oligodeoxynucleotide is similar to that of one strand of a B-form DNA (right; to clearly show the B-form conformation, the complementary strand (blue) has been modeled into the complex; this view is slightly rotated from that of the left panel). The surface of the binding groove complements that of single stranded DNA but does not allow a DNA duplex to bind (right; note that part of the complementary strand sterically clashes with the protein). Thus, the structure also explains the requirement for a single-stranded region for topoisomerase III activity.

A comparison of the cocrystal structure with that of the apo enzyme reveals that upon single-stranded DNA binding a conformational change occurs in the protein that allows substrate access to the active site. The conformational change also positions catalytically important residues to cleave the scissile bond, the first step in the reaction catalyzed by topoisomerase III. These results identify key structural elements in understanding the action of the enzyme.

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