The structure of topoisomerase I, determined by crystallography, is the fruition of a Herculean effort (*3*, *4*). Indeed, the authors present three separate structures, each of which is of a complex between the human protein and a segment of duplex DNA. Two of these show how DNA is bound noncovalently by an enzyme that is rendered inactive by mutation of the active site tyrosine. The third complex uses active enzyme but a modified duplex that is made with a bridging phosphorothioate, a diester that can be cleaved by the enzyme to yield fragments that are defective in rejoining (*8*); this strategy results in a cocrystal of the covalent complex. In all three cocrystals the protein completely encircles the duplex like a nut around a bolt. Within this cavity, the amino acids in contact with the scissile phosphodiester are exactly as would be expected for the active site of a topoisomerase: Basic residues are positioned around the phosphate to enhance its reactivity and a tyrosine hydroxyl is positioned to attack it. The protein also contacts several nucleotides that flank the scissile phosphate. Perhaps because almost all the interactions are with the backbone and not the bases, the DNA is largely undistorted, closely resembling standard B-form DNA. Most important, the contacts to one side of the broken phosphodiester are neither numerous nor intimate. This suggests to the authors that topoisomerase I transiently loses hold of this "downstream" segment and that topological change occurs as this loose strand rotates relative to the "upstream" duplex. This mechanism is quite different from that deduced from biochemical and structural experiments for topoisomerase II (*7*) and the prokaryotic homolog of topoisomerase III (*6*). Here, both ends of the break are held by the enzyme, which then opens like a pair of jaws to let another DNA pass through the break before it is resealed.

Although the overall structure of topoisomerase I is novel, parts of the protein look like portions of other proteins. For example, two of the subdomains that encircle the DNA closely resemble structures found in bacteriophage integrases (although the sequence similarity is vanishingly small between these families). Integrases are biologically distinct from topoisomerases; they act on pairs of duplexes and transfer strands from one to another. Nevertheless, the basic chemistry of strand cleavage and rejoining is identical for integrases and topoisomerase I (*9*) and, not surprisingly, the conservation of structure is restricted to the subdomains of the catalytic site. A more unexpected structural homology is to another prokaryotic protein, Rop, that forms a prominent coiled coil. In topoisomerase I, such a coiled-coil structure juts away from the body of the protein and, although it has a positively charged surface, does not make extensive contact with the DNA duplex. Its intertwined α helices, which constitute a "linker" region between two subdomains of the catalytic core, form a notable protuberance from the body of the enzyme. Stewart *et al.* (*4*) propose that the linker acts like a brake that interacts with the DNA as it rotates during the interval between cleavage and rejoining. A similar function is also proposed (*4*) for a pair of helical "nose cones" that protrude from a different surface of the core.

Thus, topoisomerase I is expected to promote the untwisting of only a few superhelical turns of DNA in a single cycle. The number of supercoils relaxed in a single cycle has recently been measured for a viral topoisomerase that lacks a linker domain (*10*), setting the stage for a comparison with topoisomerase I. The issue is significant because the proposed braking would imply that excess (or deficient) interwindings between strands are of sufficient biological value to prompt selection for an enzymic design that removes them gradually.

These two reports will certainly stimulate a new round of experiments on enzyme mechanism, but perhaps the most important lead for biomedicine concerns structural implications for agents that inhibit topoisomerase I. The founding member of this promising family of anticancer agents is camptothecin (*5*), and Redinbo *et al.* (*3*) present a model for the way this drug binds to the topoisomerase I–DNA covalent complex. Their model nicely accounts for many of the mutations known to render topoisomerase I resistant to camptothecin and for the effect of various chemical modifications on the potency of camptothecins. In the model, the drug stacks onto the base downstream of the scissile phosphate, a feat that requires this base to flip around its glycosidic bond (*11*), thereby disrupting its Watson-Crick pairing. It seems certain that this model will stimulate a new wave of pharmaceutical design for better inhibitors of this fascinating enzyme.

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WEBWATCH

Genetic rolodex

http://bioinformatics.weizmann.ac.il/cards/index.html

GeneCards integrates subsets of information stored in big genetic databases and presents this in the form of a concise screen of data, including gene name and synonyms, gene locus, protein products, and associated disease data. With the help of "siftware," the GeneCards system automatically mines the databases to extract entries useful for quick navigation; wider or deeper searches can then be done with existing engines. Each card has a button to generate related cards, and future developments may include automated suggestions to help guide the search.

Changing landscapes

http://edcwww.cr.usgs.gov/Earthshots/

Since 1972, images from the Landsat satellite have been archived at the Earth Resources Observation Systems center of the U.S. Geological Survey. To make them available to the public, the Earthshots site has started posting these images of different locations around the world, taken at different times. A 1972 view of the Kara-Bogaz-Gol lagoon in Turkmenistan can be compared directly with the same region in 1987 to see the dramatic changes caused by decreasing water levels. Explanations of the Landsat maps are provided along with links to other sites.

The language of cells

http://www.mblab.gla.ac.uk/~julian/Dict.html

The Dictionary of Cell Biology (DCB) Web site is an Internet edition of the reference book of the same name. Hosted by the University of Glasgow, the DCB contains the entries and cross-references of the second edition print version, along with enhancements and new entries scheduled for the third edition. Users can search its 5450 entries with a keyword query or browse keywords from a simple graphical map. Returned definitions are further hyperlinked to other entries.

Edited by David Voss

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