Super Coils for Tangle-Free DNA

Snarls are certainly not characteristic of the elegant DNA double helix, as it unzips and refastens while directing the various processes of life. Yet separating two strands of a twisted rope invariably causes frustrating tangles in the remaining length. An enzyme, recently discovered and rapidly characterized in admirable detail, not only prevents DNA snarls, but reduces the energy cost of splitting the DNA molecule.

Nobody anticipated the existence of a tangle-preventing enzyme until "gyrase" was discovered two years ago by Martin Gellert, Kiyoshi Mizuuchi and colleagues at the National Institutes of Health. Reports at the Cold Spring Harbor Symposium in New York last week bound up many of the loose questions about how the enzyme operates. Both Gellert and Nicholas R. Cozzarelli of the University of Chicago described sites where gyrase attaches to DNA, the enzyme's energy requirements and the separate functions of its two subunits.

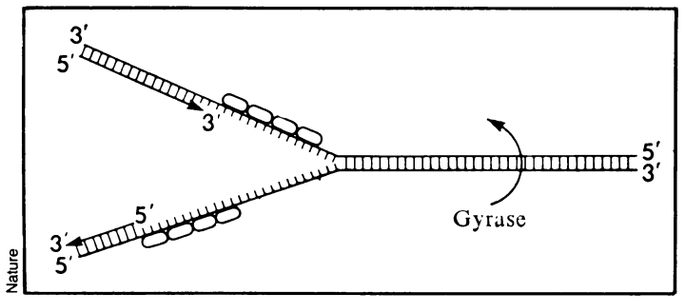
Gyrase uses energy from ATP molecules to "super coil" the DNA double helix in the direction opposite the twist of the helix. The stored mechanical energy from such super coiling makes a local region of the helix easier to open (by about one kilocalorie for each mole of nucleotide pairs separated, Gellert calculates). Gyrase also makes a temporary cut (which it also reseals) through one DNA strand. The break allows the helix to swivel and relax twists built up during strand separation.

Two drug effects previously studied helped catalyze the rapid description of gyrase. Antibiotics novobiocin and nalidixic acid were known to immediately stop the DNA replication in *Escherichia coli* and some other bacteria. Geneticists had identified the genes involved in the responses to each drug, but the means of the drug actions remained a mystery.

Gellert and Cozzarelli discovered that the two antibiotics both inhibit the action of gyrase, but in different ways. Nalidixic acid interferes with nicking-closing activity, while novobiocin acts as an energy poison, preventing use of ATP.

The researchers now have evidence that each of the two subunits is the site of one drug action, and thus they know the gene that produces each subunit. One protein chain is responsible for nicking and later resealing the DNA strand. Surprisingly, that activity requires no energy. But energy is required if the enzyme is to operate continuously.

The energy converter of gyrase is the other subunit. In the presence of double-stranded DNA, that protein chain splits ATP. Both Cozzarelli and Mizuuchi postulate that the energy is needed to move the enzyme along the DNA molecule (or to feed the DNA through the enzyme). Going even further into enzyme mechanics, James C. Wang of Harvard University has evidence that in the interaction DNA snakes continuously around the outside of the enzyme complex.



Nature

Gyrase gives double helix a new twist.

All DNA is not equal as seen by the gyrase. The enzyme prefers to bind to certain sites, according to work of both Gellert's and Cozzarelli's groups. The researchers have scrutinized a number of different DNA molecules and find sites every few thousand nucleotides. A sequence of 11 nucleotide pairs common to two (and similar to the others) was found a short distance from sites where gyrase nicks. "It looks like a common sequence dictates 'cut nearby,'" Cozzarelli says.

Gyrase so far has been best studied as an aid to replication of DNA, but recently scientists have begun investigating its potential role in RNA production. DNA strands must separate to serve as templates for messenger RNA involved in protein production.

The importance of gyrase probably varies among organisms. Gyrase seems essential to *E. coli,* and has been identified for another bacterium and virus. However, DNA replication in a laboratory system using another viral chromosome requires no gyrase. Gellert points out that the question is still wide open whether gyrase functions in higher organisms. Researchers have identified several other processes that can contribute to the energy required for DNA helix unwinding. To meet the problems of twisting, swiveling and exposing sections of their lengthy chromosomes, various other organisms probably require different balances of DNA separation aids. □

HEW asked to regulate gene splicing

With legislation regulating recombinant DNA research stalled in both the House and the Senate, last week six senators wrote to Joseph A. Califano, secretary of Health, Education and Welfare, suggesting that executive orders from his department, rather than legislative action, could be invoked to correct deficiencies in the present system of regulation, the guidelines formulated by the National Institutes of Health.

Edward M. Kennedy (D-Mass.), Jacob J. Javits (R-N.Y.), Gaylord Nelson (D-Wis.), Adlai E. Stevenson (D-Ill.), Harrison A. Williams Jr. (D-N.J.) and Richard S. Schweiker (R-Pa.) cited three reasons for their support of executive action by HEW: Evidence accumulated during the past year indicates that recombinant DNA research, if properly controlled, is safe, at least in those cases tried, and congress may be reluctant to pass legislation regulating research that is not a clear hazard to public safety; the legislative load is so heavy that Congress may not pass any legislation regulating recombinant DNA research this session; the NIH guidelines, which are constantly being updated as evidence of the safety of various kinds of recombinant DNA research is gathered, have proved "properly cautious," but need to be extended. This extension can possibly be better and more rapidly accomplished through HEW action rather than through legislation.

The aspect of the present regulation setup that the senators seem most concerned about is that privately supported research, such as that in industry, is not subject to monitoring by NIH nor to sanction for failing to comply with the guidelines. Moreover, federal agencies other than NIH comply with the regulations only voluntarily. Finally, the senators feel that the responsibility for enforcement of the NIH guidelines should be transferred from NIH, the principal federal sponsor of recombinant DNA research, to HEW.

The senators urged Califano to try to regulate industry through existing powers of the Food and Drug Administration or through use of a Public Health Service act that deals with possible communicable diseases.

Califano has not yet replied. □