exchange. They chose a particular type of DNA strand exchange reaction, namely, that between supercoiled duplex DNA and single-stranded DNA complementary to one of the strands in the duplex. This reaction has a unique advantage: It is driven forward by the free energy of DNA supercoiling (see the figure). Indeed, at elevated temperatures (but still below the melting temperature of DNA), these reactions can proceed spontaneously without participation of any proteins (*4*). This temperature elevation is necessary for the initiation of spontaneous strand-exchange reactions, suggesting that premelting changes in the single-stranded DNA or supercoiled duplex DNA are necessary for the homologous pairing.

RecA protein can promote pairing between these DNA molecules at temperatures well below the threshold point of the spontaneous reactions. RecA likely induces in DNA a premelting state that is necessary for homologous recognition between DNA molecules. This state probably involves a partial unstacking of DNA bases. So it follows that the 20–amino acid peptide with DNA-unstacking activity could substitute for the entire RecA molecule and catalyze the reaction, although it is less efficient than RecA (*1*).

If a small peptide can mediate DNA strand exchange, what is the function of the remaining 332 amino acids of RecA? Because the reaction used by Voloshin *et al.* was energetically driven by the relaxation of torsional stress in supercoiled DNA, the peptide was not required to do too much; it needed only to initiate the strand exchange, which would then proceed further spontaneously. In natural recombination reactions in cells, DNA supercoiling will rarely drive the reaction in this way. Usually, DNA strand exchange is energetically costly—long DNA molecules have to be rotated, proteins on DNA must be removed, and the strand-exchange reaction has to pass through heterologous regions that are not well paired. Whole RecA protein hydrolyzes adenosine 5′-triphosphate (ATP), and the energy so harnessed drives the strand exchange reaction (*5*). The protein domains that convert chemical energy into a directed motion are certainly bigger than 20 amino acids. There are also probably many other domains that are needed for the full activity of RecA—for example, domains that contact LexA repressor during proteolytic cleavage, a reaction necessary for the response of the cell to DNA damage (*6*). Thus, in real life RecA needs all of its 352 amino acids.

However, the part of RecA that helps two homologous DNA molecules to recognize each other is very likely the L2 loop, or a portion of it. Its ability to unstack DNA bases would allow RecA to stretch and unwind the DNA helix. A yeast recombination protein, Rad51, and its human analog also stretch and unwind DNA (*7*); these additional examples of a stretched DNA structure facilitating homologous recognition of identical sequences point to a universal mechanism of homologous recognition. When protein-free DNA is stretched by an external force, there is a transition from the classical Watson-Crick structure to the stretched form, with a roughly 50% extension of the length (*8*). This increase corresponds to the DNA extension in filamentous RecA-DNA complexes (*9*). Perhaps RecA, by binding to DNA, uses its L2 region to induce a structural transition in DNA from a regular helix to the stretched configuration.

Until now, experiments with the whole RecA protein could not reveal the mechanism by which RecA stretches and unwinds DNA. Now that Voloshin *et al.* have identified the active core peptide of RecA that can cause stretching and unwinding, the field of DNA recombination should soon know exactly how two homologous DNA molecules recognize each other before they exchange their genetic material.

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Dengue Hemorrhagic Fever

Anthony A. James

An alarming emerging disease is caused by dengue viruses, which have escaped their original home in Asia to spread to the tropical Americas. Dengue infection, usually resulting in flu-like symptoms, now sometimes causes a much more dangerous illness—dengue hemorrhagic fever, also known as dengue shock syndrome—which can be fatal in infants and young children (*1*). Thus, the new results of Olson *et al.* in this issue of *Science* (*2*) are particularly welcome; they give hope that we may be able to control dengue fever by genetically altering the organism that transmits the disease, the mosquito.

Most research on dengue virus has focused on vaccine development and on better methods of eradicating mosquitoes. But a more promising approach may be to engineer mosquitoes so that they can no longer transmit disease. If mosquitoes that have been engineered to be resistant to the virus are released into the natural population, they should decrease the transmission of the disease. To accomplish this, a three-pronged approach is necessary: We must (i) be able to genetically engineer mosquitoes in the laboratory, (ii) know how to move the genes into mosquito populations in the wild, and (iii) understand the population genetics and transmission properties of the target mosquitoes.

The results of Olson *et al.* are an important step in successfully constructing mosquitoes that cannot transmit disease: their results provide a proof-of-principle that we can really block dengue transmission by genetic engineering. Olson and co-workers (*2*) have used a Sindbis virus to express an antisense RNA derived from the dengue viral genome in the mosquito *Aedes aegypti*. The presence of this antisense RNA in the mosquito prevents dengue infection of the salivary glands and halts subsequent transmission of the virus.

This strategy of creating "intracellular immunity" is the first successful effort to express an exogenous gene that confers resistance to an important human pathogen. Nevertheless, more needs to be done. The new Sindbis viral constructs are not permanently integrated into the mosquito genome, so the resistance to dengue virus cannot yet be passed down to new generations of mosquitoes. But when this hurdle is overcome, these dengue-resistant mosquitoes can be tested in field trials for effectiveness in real-world situations.

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The author is in the Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92717, USA. E-mail: aajames@uci.edu