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A NEW TWIST TO TRANSCRIPTIONAL CONTROL

NEW ORLEANS—Protein activators can specify transcriptional initiation by helping RNA polymerase "see" its binding site. This new regulatory motif was described by Martin Rosenberg (Smith Kline & French Laboratories, Swedeland, PA) at this year's *Bio/Technology* conference.

Rosenberg and his coworkers have been studying the product of the *c*II gene of bacteriophage lambda. The *c*II protein is a transcriptional activator. It works at three promoters to control genes necessary for lysogenic development. The best known gene under its control is the repressor. When *c*II binds to DNA it encourages the subsequent attachment of RNA polymerase—as does repressor. The two proteins stimulate polymerase binding in very different ways, however.

In a series of experiments reminiscent of the "helix swaps" between the repressors of lambda-like phage 434 and the *Salmonella* phage P22, Rosenberg was able to change the specificities of *c*II and its P22 equivalent. But unlike the 434 experiments, which involved switching DNA binding domains of the two *proteins*, Rosenberg altered the activities by switching a six-nucleotide sequence that lies within the promoter's recognition site.

Yen-sen Ho, in Rosenberg's laboratory, showed that both *c*II and the P22 protein recognize a DNA sequence containing a direct repeat of the tetranucleotide TTGC, separated by six bases. The tetranucleotides flanking the core sequence lie on the same side of the helix and are the binding sites of the activator. RNA polymerase makes its contacts with the core sequence on the helix's other face. Apparently, the two proteins sandwich the DNA between them. The P22 protein and *c*II can each bind to the other's promoter, through the identical tetranucleotides, but fail to activate the heterologous promoter once bound.

Remarkably, when Susan Kielty exchanged the core sequence from P22 for the hexanucleotide of lambda, she found that the P22 protein could now activate the lambda promoter. Thus, these workers showed that promoter specificity can be determined by how the activator *presents* the binding site to polymerase. This is in sharp contrast to other systems, where specificity is conferred by selective binding of the activator.

Perhaps even more surprising, it appears that in order for *c*II to bind to DNA at all the helix must literally bend over backwards. Because the protein recognizes a direct repeat sequence in the DNA—and presumably retains a dyad symmetry in its oligomeric structure, analagous to other regulatory proteins—it is difficult to make models of the protein-DNA complex without bending the DNA more than 90 degrees. This had been considered unlikely, if not impossible. However, a recent paper from Don Crothers' group at Yale (*Cell* **47**:995–1009, 1986) indicates that this is exactly what happens when the cyclic AMP activator binds to DNA.

Rosenberg believes *c*II bends DNA in the same way. He suggests this bending properly aligns the polymerase binding site and thereby activates transcription.

—Harvey Bialy

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