companied by 9 to 12 m of surface displacement along the Carrizo segment have formed the cornerstone of the characteristic earthquake model for the San Andreas fault (*1*, *3*, *5*, *7*). The Carrizo segment was hypothesized to rupture only in large-magnitude events similar to the characteristic 1857 earthquake. Recent studies reveal a more complex history of earthquakes in the Carrizo Plain. A cluster model has been proposed to describe irregular recurrence times for Carrizo earthquakes, and recent studies show that the amount of displacement per earthquake has varied substantially (*10*). In addition, it appears that some Carrizo earthquakes have been smaller in magnitude or had a significantly different rupture pattern than the characteristic 1857 earthquake (*10*). The more complex rupture patterns revealed by recent research on this section of the San Andreas are difficult to explain with a simple characteristic earthquake model.

More than a decade of research results are allowing scientists to piece together parts of the San Andreas earthquake puzzle. In my view, the incomplete picture that is emerging is inconsistent with repeated, predictable characteristic earthquakes. The model may indeed be useful as a convenient way to try to understand nature, but its usefulness in routine methods of seismic hazard assessment should be reevaluated. We need physical models that better explain the observed irregularities in fault rupture. In any case, there is cause for enthusiasm among earthquake scientists because the acquisition of sufficient data to test the characteristic earthquake model is, in itself, a major step toward the larger goal of understanding earthquakes. As additional pieces are added to the earthquake puzzle, a clearer picture will emerge.

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Transcription Factor IIA: A Structure with Multiple Functions

Raymond H. Jacobson and Robert Tjian

Millions of years of evolutionary pressure ensured that the readout of the genome—transcription and gene expression—is tightly regulated. In metazoans, the core transcriptional machinery responds to multiple signals, which trigger cascades of gene expression that ultimately lead to the proper formation of an embryo. How does the transcription machinery transduce and integrate the vast repertoire of converging signals to correctly increase or decrease messenger RNA production from a particular gene? An important way station on the route to answering this central question is reported in this issue of *Science*. Geiger and co-workers have solved the crystal structure of a core component of the transcription machinery (*1*)—a complex of DNA, TATA-binding protein (TBP), and transcription factor (TF) IIA.

In eukaryotic cells, RNA polymerase II and its associated factors (general initiation factors TFIIA, -B, -D, -E, -F, and -H) form a large structure, containing some 40 to 50 proteins, that initiates accurate transcription. Despite this enormous complexity, a remarkably detailed understanding of transcription by RNA polymerase II has been revealed by two decades of biochemical fractionation and in vitro–reconstituted transcription reactions. Crystal structures of TBP complexed with the TATA DNA element gave us a first glimpse of the architecture of the complex as it exists before initiation of transcription (the preinitiation complex) (*2*, *3*). TBP impressively deforms the promoter DNA by introducing a sharp bend and a dramatic widening of the minor groove. More recently, the triple complex of TBP and the general initiation factor TFIIB bound to DNA was solved—information that started to define the rules by which additional initiation factors enter into the preinitiation complex (*4*). Now the new crystal structure of a ternary complex containing general initiation factor TFIIA, TBP, and DNA (*1*) adds the next piece of the puzzle in our developing picture of the preinitiation complex.

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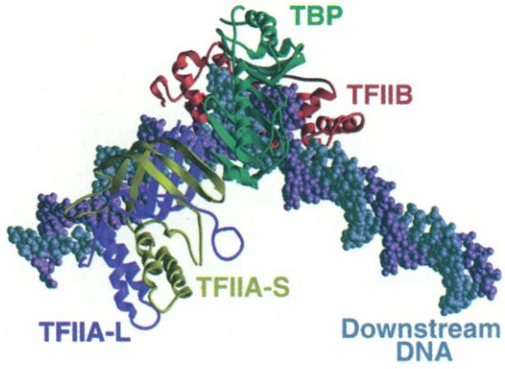
TFIIA appears to be a "coactivator," important for mediating activated transcription (*5*). Although TFIIA's exact role in transcriptional regulation is still somewhat unclear, this factor enhances the DNA-binding affinity of TBP and mediates efficient activation of transcription by various enhancer-binding proteins (*5*, *6*). The structure of the TFIIA/TBP/DNA complex reassuringly confirms TFIIA's functional assignments made on the basis of biochemical experiments. For example, it can easily be seen how TFIIA enhances the DNA-binding properties of TBP: The TBP/TFIIA complex has extended contacts to DNA (see figure). The ability of TFIIA to stabilize TBP/DNA interactions may also in part explain the derepression of basal transcription by TFIIA, although at least for in vitro transcription, TFIIA is not required.



The complex structure of the core of the transcription machinery: TBP/DNA/TFIIA/TFIIB. TFIIA has a large (L) and a small (S) subunit.

As in TFIIB/TBP/DNA, recognition of the TBP/promoter complex by TFIIA does not require further deformation of either TBP or the DNA. Only the β-barrel domain makes contacts that stabilize the protein/DNA complex, leaving the majority of the helical domain free to interact with other as yet unidentified factors. Thus, the apparent coactivator properties of TFIIA in directing activated transcription may result from direct contact between enhancer-bound activators and the exposed surfaces of TFIIA.

TFIIA activity requires expression of two genes that form a large and a small subunit. In *Drosophila* and in humans, the large subunit of TFIIA is proteolytically processed, clipped into two pieces somewhere

within the middle of the sequence (*7–9*). The ternary complex described by Geiger *et al.* includes a yeast variant of TFIIA that consists of the full-length small subunit and a large subunit with an internal deletion, resulting in a functional but truncated molecule (*10*). The two chains of TFIIA embrace to form a structure consisting of a six-stranded β-barrel and a four-helix bundle, in which half of each domain is contributed by each of the two subunits. In the absence of either the large or the small subunits, a stable globular protein is unlikely to form. Such a fold is not typical of the modular organization of most transcription factors and should alert us to the dangers of using deletion mutants to map interaction domains in the absence of structural information.

Most revealing is that only relatively small portions of TBP's exposed surface in the binary complex become buried upon formation of the ternary complex. TBP also has restricted contact surfaces in the TFIIB triple complex (*4*) and in its interactions with other basal factors (*11*). These observations suggest that factors may enter the preinititation complex by contacting rather limited regions of different subunits within the complex, relying upon the relative spatial disposition of these elements to obtain specificity. In the TFIIA ternary complex, these interactions involve specific contacts to limited regions of TBP and nonspecific interactions with the phosphate backbone of the DNA. This mode of recognition may partly explain how TBP and TFIIA can participate in multiple interactions with other components of the transcriptional machinery. Indeed, isolation of TBP-containing complexes from *Drosophila* and human cells suggest that this essential transcription factor is in a stable complex with numerous tightly associated subunits, termed TAFs, that together form TFIID. Some of the TAFs bind both TFIIA and TFIIB. Thus, the formation of an active preinitiation complex likely requires multiple contacts between TBP, TFIIA, TFIIB, and TAFs.

It is not known at present whether the promoter/preinitiation complex can form via alternative contacts between its constituents, depending upon the core promoter sequences and adjacent DNA-binding proteins. We also do not know how the TAFs interact with the TBP/DNA/TFIIA structure reported here because some of the subunits of TFIID directly contact TFIIA (*7*). As more structural information becomes available, it will become clear how other components of the basal transcription apparatus—such as TFIIE, TFIIF, and the subunits of RNA polymerase II—fit into the framework revealed by the TFIIA and TFIIB complexes and how TFIIA may transduce activation signals from enhancer-bound regulators.

It is hard to believe that only 6 years ago we had just obtained the first few components of the preinitiation complex as purified proteins that could restore accurate initiation of transcription in vitro. Now that high-resolution structures of partial initiation complexes are accumulating rapidly, we may soon have a detailed picture of the entire transcription machinery and will begin to understand how this amazing complex controls the expression of some 100,000 genes in the eukaryotic cell.

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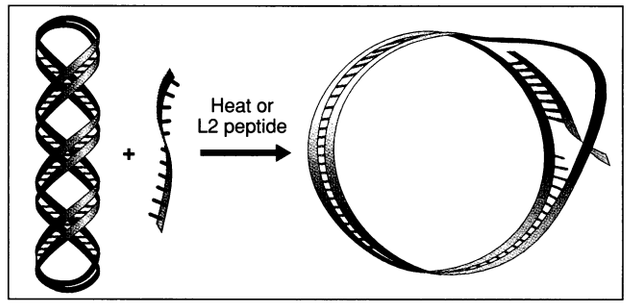
Getting Down to the Core of Homologous Recombination

Andrzej Stasiak

Can a small piece of a big enzyme perform a reaction normally catalyzed by the whole protein? It seems that the answer is yes, at least when the piece is a 20–amino acid peptide derived from RecA, a bacterial protein that repairs and recombines DNA, and when the reaction is a certain kind of DNA strand exchange. In this issue, Voloshin and coworkers (*1*) present experiments that illuminate a crucial step in homologous recombination, the process by which DNA molecules with similar genetic information line up side by side and exchange strands. Such reassortment of the genetic material creates new genetic traits in the offspring and thus drives the process of evolution.



Strand exchange between supercoiled double-stranded DNA and single-stranded DNA. The supercoiled molecule becomes relaxed as strand exchange progresses. This process of relaxation drives forward the reaction in which every opening of base pairs in the substrate duplex is compensated by formation of new base pairs in the heteroduplex region. The reaction stops when the relaxation of supercoiled DNA is attained (*4*). In this schematic drawing the primary helicity of DNA is not shown. For every 10 base pairs exchanged (one turn of DNA helix), one superhelical turn is relaxed.

In their search for the regions of the RecA protein that can mediate DNA strand exchange, these authors turned to the crystal structure of RecA, solved earlier (*2*). Although there is no DNA in these crystals, RecA monomers form helical structures that are similar in shape to RecA-DNA filaments visible under the electron microscope when RecA binds to DNA. Crystallized RecA monomers have two disordered loops, as if they were lacking stabilizing contacts with DNA. Comparison of the crystal structure of RecA with the RecA-DNA filaments (*3*) suggests that these disordered loops (L1 and L2) are in a good location to contact the DNA. Therefore, Voloshin and co-workers synthesized short peptides equivalent to individual disordered loops and assayed the activities of these peptides. One of the 20–amino acid peptides, corresponding to loop 2, was able to bind to single- and double-stranded DNA. In addition, while binding to single-stranded DNA, this peptide decreased stacking of nitrogenous bases, the building blocks of DNA, mimicking RecA's ability to stretch and partially unstack single-stranded DNA. This result is hardly surprising; after all, DNA binding domains are expected to bind to DNA, although they may show a lower affinity when taken out of the context of the whole protein.

However, the authors went further and challenged the peptide with the seemingly impossible task of catalyzing DNA strand

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