Article

15

Structure and flexibility adaptation in nonspecific and specific protein-DNA complexes.

Kalodimos CG, Biris N, ..., Boelens R, Kaptein R
Science. 2004 Jul 16; 305(5682):386-9

Evaluations

Evaluated by Jim Maher | James Hu | Antonio Rosato | Thomas Kodadek | John Ladbury

This NMR (nuclear magnetic resonance) study of lac repressor binding to a nonspecific DNA site allows a delightful comparison between features of a sequence-specific DNA/protein interaction and a sequence non-specific interaction.

Long the source par excellence of biochemical insights, the lac repressor is seen to interact only electrostatically (as predicted) with non-operator DNA, while adopting a binding geometry that is surprisingly different from in the specific complex.

The result confirms predictions from classic studies of salt-dependence and suggests how the degree of macromolecular interface dehydration may distinguish specific and nonspecific complexes.

Competing interests: None declared

Cite this evaluation

Evaluated by:
Jim Maher
Mayo Clinic College of Medicine, USA
Structural Biology
16 Aug 2004

Rating 8
Must Read

This paper examines an important aspect of gene regulation that is often neglected: the binding of transcription factors to nonspecific DNA.

Kaptein and coworkers use NMR to examine the binding of a dimeric lac repressor headpiece to a nonspecific DNA fragment.

By a combination of structure determination, dynamics, and H-D exchange, they probe the differences between free repressor, the nonspecific complex, and the operator-bound complex. The similarities and differences, which include a rotation of the protein relative to the DNA that preserves some protein-DNA contacts while reorganizing others, provide a detailed look at the binding reaction. In addition, comparison of the structures and dynamics allows some interesting suggestions about the molecular basis for the heat capacity change for DNA binding.

Competing interests: None declared

Cite this evaluation

Evaluated by:
James Hu
Texas A & M University, USA
Chemical Biology
29 Jul 2004

Rating 8
Must Read

The present work is a brilliant example of a structural biology investigation that only NMR can make successful.

In previous work, the authors studied the structural and dynamic properties of the lac repressor in complex with specific DNA constructs.

In this work, they now add a characterization of the interaction with nonspecific DNA. The authors propose that the interaction of regulatory DNA binding proteins with their target sites is usually preceded by binding to nonspecific DNA and that the regulatory protein then scans the DNA to search for the target site, thus resulting in a very efficient process. A large ensemble of NMR data constitutes the experimental basis for the authors' propositions. These include the solution structures of a dimeric lac repressor DNA binding domain with both specific and nonspecific DNA. In addition, the analysis of protein dynamics at the protein-DNA interface, obtained through different NMR techniques, shows that the protein interface remains flexible until it gets to the target site, where it locks into the conformation that is best for binding. Protein flexibility is thus key to the efficiency of the whole process.

Competing interests: None declared

Cite this evaluation

Evaluated by:
Antonio Rosato
University of Florence, Italy
Structural Biology
28 Jul 2004

Rating 8
Must Read

This paper contributes important structural and dynamic information relevant to how sequence-specific DNA-binding proteins distinguish specific from non-specific sites.

A NMR study of the structure and dynamics of a complex between a fragment of the lac repressor and a non-specific 18 base pair oligonucleotide is reported.

Comparison of these data with the specific DNA complex reveal a number of interesting details of how the specificity-determining residues in the protein interact in a different way with specific and non-specific sequences, which is very different from the simple view that these residues simply do not recognize non-specific sequences at all.

Competing interests: None declared

Cite this evaluation

Evaluated by:
Thomas Kodadek
Scripps Florida Research Institute, USA
Chemical Biology
27 Jul 2004

Rating 6
Recommended

This article presents structural confirmation of earlier biochemical data on non-specific protein-DNA interactions. The key questions regarding electrostatic effects and protein conformational changes are answered. The paper is fundamental to our understanding of non-specificity and gives insight into previously determined data from biophysical analysis.

The significance of the non-specific structure in terms of addressing how specific recognition by a protein of a site on DNA occurs in the context of large oligonucleotides (i.e. sliding, intersegmental transfer or hopping - see Berg et al. Biochemistry 1981, 20:6929-48 [PMID:7317363] and Halford & Marko, Nucleic Acids Res 2004, 32:3040-52 [PMID:15178741]) can now be considered in greater detail.

Competing interests: None declared

Cite this evaluation

Evaluated by:
John Ladbury
University of Texas MD Anderson Cancer Center , USA
Chemical Biology
26 Jul 2004

Rating 8
Must Read

Classification Key Changes Clinical Practice | Novel Drug Target | Technique | Clinical Trial | Review

Cite this page