

Gregory A. Petsko

How T-bet Binds to DNA

Gabriel Brandt*, Quyen Hoang*, Ce-Feng Liu*, Dagmar Ringe*, Eun Sook Hwang[^], Laurie H. Glimcher[^], and Gregory A. Petsko[^]

* Departments of Biochemistry and Chemistry and Rosenstiel Basic Medical Sciences Research Center, Brandeis University, 415 South Street MS 029, Waltham, MA 02454-9110 USA

[^] Department of Immunology and Infectious Diseases, Harvard School of Public Health and department of Medicine, Harvard Medical School, Boston, MA 02115 USA

The transcription factor T-bet is one of the master regulators of both the innate and adaptive immune response (1). It plays a central role in T-cell lineage commitment, where it controls the Th-1 response, and also in gene regulation in plasma B-cells and dendritic cells (2). T-bet is a member of the Tbox family of transcription factors, a family that includes the TBX3 and Brachyury proteins, but T-bet coordinately regulates the expression of many more genes than other Tbox proteins. A central unresolved question for master transcription regulators like T-bet is how a single protein molecule is able to bind to both a promoter recognition element on one gene, and a recognition element on a second gene or an enhancer element, either of which may be located thousands of base pairs away (3,4). We have determined the three-dimensional structure of the Tbox DNA binding domain (DBD) of T-bet in complex with a 24 base pair palindromic consensus DNA recognition site, by the method of X-ray crystallography. The structure of the T-bet DBD-DNA complex differs dramatically from that of the other Tbox proteins whose structures have been determined. Two different fluorescence-based assays confirm that T-bet binds DNA in solution in the same manner as that observed in the crystal structure. Mutational analysis of conserved tyrosine residues in T-bet is also consistent with the observed structure. We present a looping model for transcriptional regulation by T-bet that explains how one transcription factor recognizes distinct genetic elements (5), either a promoter site and a distant enhancer site, or promoter sites on two different genes, as has been suggested for so-called “transcriptional factories” (6).

References

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