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Role of protein structure and the role of individual fingers in zinc finger protein–DNA recognition: a molecular dynamics simulation study and free energy calculations

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Abstract
Molecular dynamics and MM_GBSA energy calculations on various zinc finger proteins containing three and four fingers bound to their target DNA gave insights into the role of each finger in the DNA binding process as part of the protein structure. The wild type Zif 268 (PDB code: 1AAY) gave a ΔG value of −76.1 (14) kcal/mol. Zinc fingers ZF1, ZF2 and ZF3 were mutated in one experiment and in another experiment one finger was cut and the rest of the protein was studied for binding. The ΔΔG values for the Zinc Finger protein with both ZF1 and ZF2 mutated was +80 kcal/mol, while mutating only ZF1 the ΔΔG value was +52 kcal/mol (relative to the wild type). Cutting ZF3 and studying the protein consisting only of ZF1 linked to ZF2 gave a ΔΔG value of +68 kcal/mol. Upon cutting ZF1, the resulting ZF2 linked to ZF3 protein gave a ΔΔG value of +41 kcal/mol. The above results shed light on the importance of each finger in the binding process, especially the role of ZF1 as the anchoring finger followed in importance by ZF2 and ZF3. The energy difference between the binding of the wild type protein Zif268 (1AAY) and that for individual finger binding to DNA according to the formula: $\Delta\Delta G_{\text{linkers, otherstructuralfactors}} = \Delta G_{\text{zif268}} - (\Delta G_{\text{F1+F2+F3}})$ gave a value = −44.5 kcal/mol. This stabilization can be attributed to the contribution of linkers and other structural factors in the intact protein in the DNA binding process. DNA binding energies of variant proteins of the wild type Zif268 which differ in their ZF1 amino acid sequence gave evidence of a good relationship between binding energy and recognition and specificity, this finding confirms the reported vital role of ZF1 in the ZF protein scanning and anchoring to the target DNA sequence. The role of hydrogen bonds in both specific and nonspecific amino acid-DNA contacts is discussed in relation to mutations. The binding energies of variant Zinc Finger proteins confirmed the role of ZF1 in the recognition, specificity and anchoring of the zinc finger protein to DNA.

Keywords Zinc finger · DNA binding · Protein · Specificity · Binding energy · Mutants · Molecular dynamics

Introduction

Zinc finger (ZF) structure depends on the zinc-coordinating residues as well as three conserved hydrophobic residues, the structure can adopt a wide range of amino acid substitutions which make it a potential target for design of mutant proteins, both experimentally and theoretically. These features give the zinc finger protein a great flexibility to bind various DNA base combinations, which makes it an especially good model for design of DNA binding proteins with new and varying specificities [1, 2]. A typical zinc finger DNA binding protein contains two or more zinc fingers [3]. The alpha helices in each finger interact with 3 base pairs (at least) on the DNA, interacting with 3 contiguous base pair recognition sites. Specific residues in the domain interact with specific bases, a typical binding mode is shown in Fig. 1. In the established canonical model arginine (R) in the first position preceding the alpha helix (position −1) specifically interacts with G in a particular position whereas histidine in position 3 is specific for G or A at a particular position and R6 binds G. Aspartic acid (D) in position 2 makes contacts with C or A on the secondary (5′) sequence.

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