BZip transcription factors modulate DNA supercoiling transitions – potential transcription regulatory mechanism: insights from molecular modelling

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Abstract

Torsional stress on DNA, introduced by molecular motors when the molecule undergoes under- or overtwisting, constitutes an important regulatory mechanism of gene expression [1].Torsional stress can modulate specific binding of transcription factors to DNA, introduce local conformational changes that facilitate opening of promoters and nucleosome remodelling [1,2]. Using all-atom microsecond scale molecular dynamics simulations together with a torsional restrain [3,4] that controls the total helical twist of a DNA fragment, we study the impact of torsional stress on MafB-DNA complexation. MafB (PDB ID: 4AUW)[5] is a representative of human bZIP family of transcription factors, which recognizes the palindromic DNA sequence (TGCTGACGTCAGCA). We over- and underwind free DNA and DNA in complex with MafB by 5◦ per dinucleotide step, and monitor the evolution of the protein-DNA contacts at different degrees of torsional stress. Our computations show that MafB changes the DNA sequence-specific response to the torsional stress; the dinucleotide steps that are anticipated to absorb most of the stress become more torsionally rigid as these are involved in the specific protein-DNA contacts. Also, the protein undergoes substantial conformational changes to follow the DNA deformation and maintain, at all times, the specific contacts with DNA. This results in an asymmetric increase of the free energy cost of twisting molecular transition, with respect to fee DNA, where overtwisting is significantly energetically unfavorable. Our data suggest that MafB could act as a "torsional stress insulator" creating a suitable topological environment that can, among all, promote cooperative binding of other TFs.

References

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